The New England
Journal of Medicine

VOLUME 214 MAY 14, 1936 NUMBER 20

THE HYPOPHYSIS AND METABOLISM*

BY BERNARDO A. HOUSSAY, M.D.‖

FUNCTIONALLY the most important of the four parts of the pituitary is the chromophile (principal, distal or anterior**) lobe. Its functions may be classified provisionally as (1) *morphogenetic* (growth and metamorphosis), (2) *endocrine stimulating and regulating* (development and maintenance of the gonads, thyroids, adrenal cortex, parathyroids, thymus† etc.), (3) *sexual and reproductive* (development and maintenance of the gonads and their functions, the sexual characteristics, breasts and milk secretion, etc.), (4) *metabolic* (either directly or indirectly by its action on other endocrine glands). The sexual functions are really endocrine and belong in class 2, but they have been placed in a separate group because of their special importance. This classification‡ is simple and elastic, but obviously it is not perfect.

The anterior pituitary lobe, because of its actions on growth, metabolism§ and the endocrine glands, *is necessary for the development and maintenance of the individual in a normal state:* because of its sexual and reproductive actions *it is necessary for the maintenance of the species.* It is the central and directing organ in the endocrine constellation, since its presence is required for the development and maintenance of the other glands. In some cases the latter also have an influence on the pituitary.

The posterior or neuro-intermediate lobe provides extracts of marked pharmacological activity, but its functional rôle is inferior to that of the principal lobe. Its functions of melanophore dilatation, maintenance of the capillary tone and arterial blood pressure, and regulation of water elimination through the kidneys are well known in amphibians, but the vasotonic, renal and oxytocic functions, have not yet been proved with certainty in mammals and its rôle has yet to be precisely established.

To be certain of the existence of a pituitary function it is not enough to observe the pharmacological action of an extract. The following conditions must be fulfilled: (1) a deficiency must be produced by extirpation of the gland; (2) this deficiency must be compensated for by graft, implantation or extract of the gland (or of the part under observation); (3) an excess of extract must cause phenomena* opposite to those of insufficiency. Since the pituitary is the central organ in the endocrine system, certain of its actions are due to its influence on other glands. This is shown by: (1) extirpation of any gland under consideration produces a similar insufficiency, but greater than that produced by hypophysectomy; (2) neither correction of the insufficiency nor hyperfunction is obtained by administration of pituitary extract if the said gland has been previously removed.

Until recently attention was mainly fixed on the growth, sexual and endocrine functions of the pituitary but in my opinion the metabolic functions are of great importance, as in the case of the other endocrine glands.

In this lecture I cannot attempt to describe all the extant knowledge concerning the pituitary and metabolism. I must content myself with mentioning the work contributed by my Institute which is very incompletely known, owing to difficulties of language and to the unfortunate tendency in almost all countries for workers to confine themselves to the literature in their own language. This of course, as is shown by the generous invitation given me, does not apply to Harvard University.

We have made a detailed study in one species, the dog, which permits us to correlate the numerous data we have obtained in various species with each other.

BASAL METABOLISM AND SPECIFIC DYNAMIC ACTION

The action of the anterior pituitary on basal metabolism is essentially through the thyroid. Hypophysectomy causes an atrophy of the thyroid epithelium (whose cells become flattened) and provokes hypothyroidism with lowering of the metabolism. Of the twenty-seven hypophysectomized dogs in which the basal metabolism

*This and the following paper comprise the second and third lectures in the Dunham Lectureship Series delivered at the Harvard Medical School in November, 1935. Since they deal with related subjects, they are published together. The references for both papers appear on page 982.

**In some species, e.g., amphibia, it is posterior.

†It may or may not be an endocrine gland.

‡This is a classification according to functions, not hormones, the number of which is not taken into account.

§In the amphibia, which I have studied, lack of the principal lobe produces progressive metabolic disturbances, accompanied by neuromuscular asthenia ending in death. In mammals, death due to hypoglycemia or cachexia may be observed.

‖Houssay, Bernardo A.—Professor of Physiology, Faculty of Medical Sciences, University of Buenos Aires, 1919-. For record and address of author see "This Week's Issue," page 946, issue of May 7.

*To affirm with certainty the existence of a pituitary function in man the following facts must be established. (1) Anatomico-clinico-functional phenomena (acromegaly, basophilism, hypopituitarism, etc.). (2) Removal or destruction of the gland (surgery or x-rays, etc.) must moderate the symptoms of hyperfunction or produce the syndrome of hypofunction. (3) Properly prepared pituitary extracts must compensate the deficiency and when given in excess should produce symptoms similar to the pathological hyperfunction. Without these concurring observations it is not possible to affirm the existence of a suspected function. Isolated pharmacological data are insufficient.

has been measured and that have been published up to date, twenty-two were prepared and studied in our Institute.[1, 2, 48, 49, 50, 53, 54, 55, 117] The metabolism was diminished (average 16 per cent) in all except three, in which there was no decrease. These three dogs were the only ones which had a high columnar epithelium in the thyroid.

In the rat we found, like Collip, an average decrease of 24 per cent. In the toad no metabolic decrease occurred except when there was advanced asthenia.*

In hypophysectomized dogs there is thyroid insufficiency but not athyroidism because if the thyroid gland is removed there is a further metabolic decrease reaching to 24 per cent. On the other hand the metabolic decrease in thyroidectomized animals (average 24 per cent) is not modified by hypophysectomy.

Tuberal lesions caused a decrease in the metabolism in eleven of the twenty-two dogs studied up to date (eleven by Grafe and his collaborators, eleven in our Institute by Mazzoco;[117] Solari[183]). It is probable that in these cases, as in others, the tuberal lesion diminishes or inhibits the thyrotropic action of the anterior pituitary, but in several animals there was no atrophy of the thyroid epithelium. It is also possible that the tuber has a direct action on the pituitary or on other mechanisms.

A rise in metabolism occurs on injection of anterior pituitary extracts which have a thyrotropic action, the degree of rise depending on the species studied.† In the experiments of Artundo and Solari[4] and Houssay and Artundo[53, 54, 55] in both normal or hypophysectomized dogs there was a metabolic increase of between 28 and 62 per cent, accompanied by hyperactivity of the thyroid (high epithelium, liquefaction and reabsorption of colloid) and by signs of hyperfunction (tachycardia, polypnea, slight rise in temperature, loss of weight, polyuria). These phenomena do not occur if the injected animal is already thyroidectomized‡, although some animals have a slight metabolic increase and others a diminution.[51, 52, 54]

We have not studied the habituation that is observed with prolonged treatment. In these cases a gradual decrease in metabolism which falls below the normal is seen and an antithyrotropic substance appears in the blood. (Anderson and Collip, Collip, etc.). In this connection it must be remembered that other anterior pituitary extracts depress metabolism. (Falta, Verzar, Magistris, etc.)

The specific dynamic action in twenty hypophysectomized dogs was found to be equal to that seen in normal animals.[1, 2, 55, 117*] There is a slight decrease in the specific dynamic action after thyroidectomy, which is more pronounced if the pituitary is also removed.[55]

In conclusion: the anterior pituitary has an indirect tonic action on basal metabolism through its influence on the development and maintenance of the thyroid gland.

WATER METABOLISM

It is impossible even to mention all the complex problems presented by the physiological and pharmacological actions of the pituitary on different aspects of water metabolism, so I will confine myself almost exclusively to the results of work done in our Institute.

Hypophysectomy almost always causes an intense polyuria† in dogs, rats and toads within a few hours of operation. This polyuria is transient in the great majority of dogs, and the rate of formation and the composition of the urine return to normal very soon,[88] possibly because the tuberal part remains. From the time of recovery from the initial polyuric stage, water administered is eliminated either with slight retardation[81, 82, 83] or else normally. (Reforzo, unpublished results.)

Lesions of the tuber cinereum produce an intense polyuria which is frequently transient but at times permanent.[38, 73, 98, 99, 130, 131, 140, 144, 166, 178, 179, 181, 194, 254, 313, 421, etc.] This phenomenon seen by Aschner[140] and amply studied by Camus and Roussy[178, 179] has been confirmed many times in our Institute. Polyuria is observed only when the region in the neighborhood of the tuber cinereum is damaged. It does not occur if the lesion is produced outside this zone, as, for example, in the base (Houssay and collaborators, 1915-20) or in the dorsal surface of the brain.[100] (Fig. 1.) The polyuria occurs even when the pituitary appears to be histologically normal. This tuberal polyuria can be obtained experimentally in dogs,[38, 72, 73, 98, 99, 130, 131] toads,[80, 124] sometimes in rabbits,[33] rats,[369] pigeons[371, 372] and is also seen in man in cases with pathological changes.[167, 306, 307, 313, etc.]

The tuberal polyuria occurs in dogs with previously denervated kidneys[72, 99, 144, 175] or after the splanchnics have been cut and the lumbar sympathetic chain extirpated[131] and also when the liver and pancreas have been denervated. (Rubio.[131])

There may be lesions in various of the hypothalamic nuclei in animals suffering from polyuria, but the only constant lesions are those of the tuberal nuclei. (Ramirez Corria,[125] confirming Camus, Gournay and Le Grand,[177] Gournay.[248])

*In other batrachians a decrease has been observed. Observations at different temperatures should be repeated.

†Biasotti, by nasal insufflation of the acetone extracted powder of anterior pituitary lobe in some human cases, obtained an increase in basal metabolism and polyuria; in others this result was not obtained.

‡Care must be taken to verify that only the parathyroids remain and that no thyroid tissue has been left.

*This statement is made without reference to what may occur in man, since we have not studied the latter species.

†Confirmed by numerous workers since it was discovered by Vassale and Sacchi[420] in the dog.

Polyuria usually precedes polydipsia and is seen even if the animal is deprived of water. The animals suffering from polyuria may be distinguished from the controls in water deprivation experiments by the fact that the diuresis is more prolonged, the density of the urine increases later and the blood becomes more concentrated.

Posterior lobe extract usually has an oliguric action in normal animals[41, 72, 90, 144, 175] and also in animals in which the kidneys have been denervated.[79, 383] In certain conditions, however, it acts as a diuretic.[41, 384, 385]

Posterior pituitary lobe extract diminishes or counteracts experimental or pathological polyuria insipida but its action is only transient, particularly if the polyuria is very intense. (Houssay and Hug.[81, 82, 83])

The experiments of Verney[428] and Brull[169, 170] favor the theory that a pituitary secretion physiologically modifies normal diuresis and that its absence causes polyuria. When blood of a heart-lung-kidney preparation is diffused through the head of a dog it causes a decrease in polyuria and an increase in the elimination of chlorides. Perfusion through the pelvis and hind legs has no effect. If, however, the pituitary has been previously extirpated, perfusion through the head also fails to check the polyuria.[428] Hypophysectomy in a few hours causes polyuria and fall in chloride excretion which pituitrin corrects.[169] If the blood vessels of a kidney are united to those of a polyuric dog, it secretes dilute urine, but if the irrigation is changed for that of a dog with intact pituitary the kidney secretes more concentrated urine.[170, 189]

It is therefore probable that tuberal polyuria is to be attributed in great part to an inhibition of the kidney-regulating secretion of the posterior pituitary.

The results we have obtained with toads in

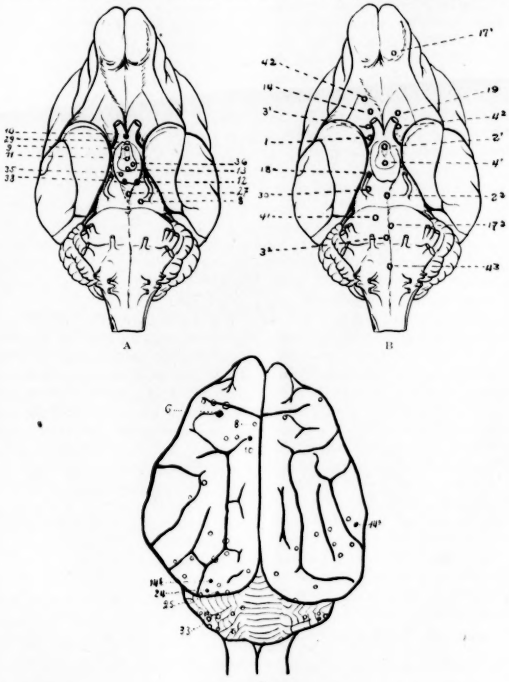

FIG. 1.

Drawings of a dog's brain showing the positions of piqûres which resulted in diabetes insipidus, A, and of those which did not alter the water metabolism, B and C.

our Institute are of great interest. Polyuria may be produced in toads of the species *Bufo arenarum* Hensell, as was observed by Houssay, Giusti, and Goñalons.[80] This was carefully analyzed by Pasqualini (work being published) and shown to be due to insufficiency of the neuro-intermediate lobe affecting especially the renal function. In toads polyuria occurs in 70 per cent of total hypophysectomies, in 33 per cent where the principal lobe is extirpated,* and in 20 per cent where there are diencephalic lesions (of the *infundibular lobe* or of the *pars basilis lamina terminalis*). In the first two groups it is immediate, progressive, intense and persistent; in those with diencephalic lesions the polyuria is transient.

The renal origin of the polyuria, through a deficiency of neuro-intermediate secretion, is suggested by the following facts: 1. The polyuria persists even when the animal is deprived of water until urine secretion ceases. 2. From the moment the diuresis ceases the animal loses weight by evaporation until the final rate of evaporation equals that in controls. 3. Water injected into the abdomen is eliminated more rapidly in the hypophysectomized animal. 4. If the ureters are ligated, cutaneous absorption of water is equal both in hypophysectomized and control animals. 5. The neuro-intermediate lobe and pitressin will stop the polyuria. With very large doses oliguria or anuria may be produced. 6. These results may be observed in animals deprived of water and with or without injection of water into the peritoneum. 7. Large doses of neuro-intermediate lobe extract have another action completely apart from the renal. This consists in the production of edema, with a great increase in weight, in both normal and nephrectomized animals.[5, 171, 262, 410, 411, 412, etc.] If the animal is placed in a hypertonic solution there is no such effect. Pitressin is more active than pitocin. Besides the renal action in these cases there is an increase in the permeability of the skin to water.[121] For the sake of brevity I will omit further details.

*In this case probably owing to hypofunction of the remaining neuro-intermediate lobe.

Thyrotropic anterior pituitary lobe extract causes polyuria in the dog by its thyroid stimulating action, but does not do so if the thyroid has been previously extirpated.[8, 159] It is not modified by castration, section of the splanchnics, etc.

MINERAL METABOLISM

Marenzi and Gerschman have shown that the blood plasma of hypophysectomized dogs has a diminished amount of potassium.[88, 112, 113] In eighteen dogs the average was 16.3 mgm. per 100 cc. On the other hand the calcium is normal,[34, 35, 88, 112, 116] 11.6 mgm. average in forty-seven dogs, and so is the magnesium, 2.03 mgm. in twenty dogs. No significant alterations are found in chlorine, phosphorus, sodium and CO_2. (Table 1.)

The decrease in the potassium of the plasma is not seen in thyroidectomized or pancreatectomized animals. It occurs in some dogs with tuberal lesions (average 17.2 mgm. in eight animals) probably due to a certain degree of pituitary hypofunction.

Extirpation of the pituitary and pancreas in the same dogs causes the modifications found in both hypophysectomized (decrease in potassium) and pancreatectomized (decrease in calcium, chlorides and sodium) animals. The alkali reserve, however, is only a little lowered and acidosis and ketonuria are very slight (attenuation of diabetes due to pituitary insufficiency).[113]

Alkaline anterior pituitary extract (in large doses intraperitoneally) causes an abnormal rise in the alkali reserve, and in phosphates, calcium, magnesium and potassium.* The chlorides and sodium are lowered, the latter to a less marked degree. (Table 1.) These results are not due to hyperthyroidism since, except for the hyperealcemia, they are observed in thyroidec-

*Potassium returns to normal in the hypophysectomized animals, but is not modified in the controls. It should also be remembered that diabetes develops under this treatment.

TABLE 1

MINERAL CONTENTS OF THE BLOOD PLASMA OF DOGS UNDER DIFFERENT EXPERIMENTAL CONDITIONS

Operation and Number of Dogs	Blood Sugar in Gm. per 100 cc.	Red Cell Volume	Total CO_2 Vol. %	Mgm. per Cent of Plasma Inorganic Substances					
				Cl.	P	K	Na.	Ca.	Mg.
Normal dogs (11)	0.095	43.9	48.2	389	4.18	18.9	385	11.2	2.08
Hypophysectomized dogs (9)	0.090	42.5	47.5	386	3.95	15.7	396	11.2	1.89
Tuber cinereum lesion: dogs (3)	—	51.9	48.3	389	3.77	17.1	395	11.6	1.74
Thyroidectomized dogs (6)	0.109	45.9	49.6	381	4.14	18.7	379	10.2	1.85
Normal dogs injected with glandular lobe extract (6)	0.266	42.3	53.8	325	7.88	18.8	345	12.8	2.34
Normal dogs injected with organ extracts (2)	0.135	46.2	48.1	368	3.44	17.9	388	11.1	1.83
Pancreatectomized dogs (2)	—	34.0	31.9	356	5.88	18.5	352	8.3	1.69
Hypophysectomized and pancreatectomized dogs (3)	—	33.0	54.1	296	4.18	15.2	323	8.5	1.90

tomized animals, nor have they a nonspecific effect since they are not produced by extracts of kidney and muscle. The rise in calcium is not seen in thyroparathyroidectomized animals, that is to say, when the parathyroids are missing.

The urinary elimination of phosphates is almost the same in hypophysectomized dogs as in normal animals when on a meat diet, but it is diminished more than in the normals during total fasting and the decrease is greater still when there is protein fasting.[34, 35] There is a marked decrease of phosphatase in the serum of hypophysectomized dogs. (Martinez, unpublished work.)

IODINE METABOLISM

In more than twenty-five papers, we have published the studies made in our Institute on the relation between the thyroid and the pituitary. The anterior pituitary lobe controls the development and the maintenance of the anatomical structure and functional activity of the thyroid. Extirpation of the pituitary produces atrophy and hypofunction of the thyroid while an excess of the thyrotropic substance of the anterior pituitary causes morphologic and functional overactivity of the thyroid gland.

Hypophysectomy does not modify or only slightly raises the *total* iodine in the thyroid but the *percentage* content of iodine is manifestly raised.[67] (Table 2 and fig. 2.) The iodine in

TABLE 2

IODINE CONTENT OF THE THYROIDS OF DOGS UNDER DIFFERENT EXPERIMENTAL CONDITIONS

(Mean Weight 9 Kgm.)

Operation and Number of Dogs	Total Iodine Mgm.	Iodine Mgm. per Cent	Probable Error ±	Variation % of Normal
32 Normals	0.95	63	3.7	0
17—Hypophysectomized, during first month	—	85	6.5	—
14—Hypophysectomized, 1 to 5 months later	1.12	100	7.7	+58
10—Normals, injected with glandular lobe extract	0.26	47	—	—25

the blood rises considerably during the first few days after operation and later decreases over a period of two to four weeks; after forty-five to sixty days it is always normal and remains so afterwards. (Fig. 3.) We have been able to add further results to those already published[89] and have so far studied a total of sixty-one hypophysectomized dogs, thirty-seven controls, eleven with lesions of the tuber, six without the posterior lobe, thirteen craniotomized.* Lesions of the tuber† and extirpation of the posterior lobe produce a lower initial rise in the blood iodine which is only transient. Extirpation of the thyroid causes an initial slight increase followed by a definite decrease to considerably below the normal level. We have attributed the initial rise in the blood iodine to the slight hyperthyroidism which frequently occurs during the first days after hypophysectomy. We did not obtain this initial increase in the blood

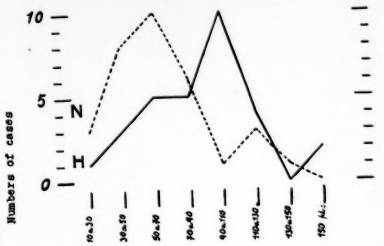

FIG. 2.

Distribution curves of normal (dotted line) and hypophysectomized (solid line) dogs on the basis of the concentration of iodine in the thyroid.

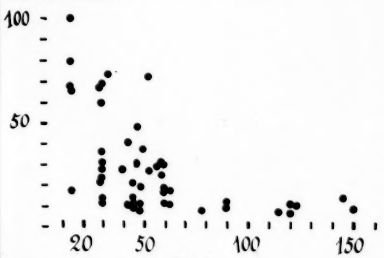

FIG. 3.

Chart showing the early rise and later fall of the blood iodine following hypophysectomy.
Abscissae—Days after hypophysectomy.
Ordinates—Mgm. iodine per 100 cc. blood.

iodine after hypophysectomy in two previously thyroidectomized dogs, which further supports our interpretation. This does not, however, explain satisfactorily why it should persist even when the thyroid is undergoing atrophy.‡

*The average blood iodine in the second series was 13 mgm. p.c.

†Sturm[416] did not find an increase when the tuber was injured.

‡Sturm[416] has confirmed the existence of an initial hyperiodemia, but he found it to be transient and accompanied by hyperioduria. He believes that the hypophysis stores iodine, sending it to the intermediate brain (rich in iodine according to Schittenhelm and Eisler,[287] and Sturm and Schneeberg[433]) which in its turn has a direct influence on the thyroid secretion and an indirect one by means of the thyrotropic hormone of the anterior pituitary. Some of his arguments are not valid, e.g., that the hypophysis is specially rich in iodine (as has been proved by Ruff); besides he is neither the first, nor the only worker to have determined the iodine content of the pituitary.[152 185 208 253 275 296 357 376 389 397 405 407 417 430 etc.

Anterior pituitary lobe extract with thyrotropic action causes a marked decrease in the total iodine of the thyroid (alcohol insoluble and thyroxine iodine)[90, 91, 185, 230, 231, 249, 250, 318, 391, etc.] and prevents an increase after unilateral thyroidectomy.[90] (Table 2.) The blood iodine, (total and alcohol insoluble), rises considerably in normal,[90, 91, 185, 249, 387, etc.] hypophysectomized or unilaterally thyroidectomized dogs with this treatment.[91] This hyperiodemia is due to the hyperthyroidism produced, since it is not obtained if dogs with total thyroidectomy are injected.[90, 91] The last-mentioned animals usually present a decrease in blood iodine (due possibly to excessive elimination or greater fixation).*

The action of the anterior pituitary on the thyroid iodine and blood iodine is undeniable but it is impossible to tell whether the gland has a specific action, either direct or indirect, apart from its effect on the thyroid.

*This suggests the possibility of another action of the extract on blood iodine, opposed to the effect of the thyrotropic hormone.

PROTEIN METABOLISM

The pituitary gland is an important regulator of the endogenous protein metabolism which it stimulates, whereas it has little influence on the exogenous protein metabolism. It also takes part in the formation of sugar from protein.

On a meat diet or the same mixed diet, hypophysectomized animals eliminate the same quantity of nitrogen per Kg. per day, as the controls.[15-24, 56-60, 140] (Table 3.) However, during the first six to seven hours after food their urinary excretion is less, with compensatory greater excretion during the remaining seventeen to eighteen hours.[15-21] If glycine is injected the curve showing its disappearance from the blood is more gradual than in the controls.[126] There seems to be a slower fixation or catabolism of amino-acids.

When fasting, hypophysectomized dogs[15-21] and toads[22, 23] only eliminate two-thirds of the quantity of nitrogen excreted by the controls. On a fat and carbohydrate diet which is protein free (i.e., protein fasting) the decrease in

TABLE 3

NITROGEN EXCRETION OF DOGS, TOADS AND RATS

Recorded in Grams Nitrogen per Kilogram Body Weight per Diem

	Hypophysectomized	Lesion of Tuber Cinereum	Normals	Per Cent of Decrease of Hypophysectomized Compared with Normals
DOGS				
Meat Diet				
Houssay and Biasotti, 1930	0.99	0.97	0.93	0
Braier, 1931	1.29	1.23	1.51	—14
" 1933	1.40	—	1.40	0
" 1933	0.92	—	0.94	0
Total Fasting				
10 days Braier, 1931	0.253	0.366	0.36	—30
Nitrogen Free Diet				
4th day Braier, 1931	0.14	—	0.24	—42
" 1933	0.16	—	0.26	—38
Total fasting 2nd day Braier, 1931	0.300	—	0.446	—32
Total fasting 3rd day, B. coli vaccine Braier, 1931	0.345	—	0.513	—33
Fasting and Phlorhizin				
Mean of 6 days Houssay, Biasotti, 1931	0.455	0.674	0.758	—40
Mean of 6 days Houssay, Biasotti, 1932	0.360	0.660	0.63	—42
Minimum protein balance with fat and starch diet Braier, 1931	0.200	—	0.300	—34
TOADS				
Total Fasting				
Braier, 1933	0.100	—	0.131	—30
RATS				
Complete Diet				
Braier, 1935	0.757	—	0.727	0
Braier, Morea, 1935	1.160	—	1.080	—
Nitrogen Free Diet				
Braier, 1935	0.205	—	0.283	—27
Braier, Morea, 1935	0.197	—	0.325	—65

catabolism is even more marked in dogs[15-23] and rats.[24] With this diet only 0.18-0.20 Gm. of protein per Kg. per day is necessary to maintain the nitrogenous equilibrium in hypophysectomized animals whereas the controls require 0.30 Gm.

Since Folin's work, creatinine excretion is considered as the index of endogenous catabolism. This is slightly diminished in hypophysectomized dogs when on a meat diet[15-21] and very slightly altered in hypophysectomized rats.[24] But during total fasting or protein fasting there is a decrease of thirty to forty per cent in both species. (Fig. 4 and table 4.)

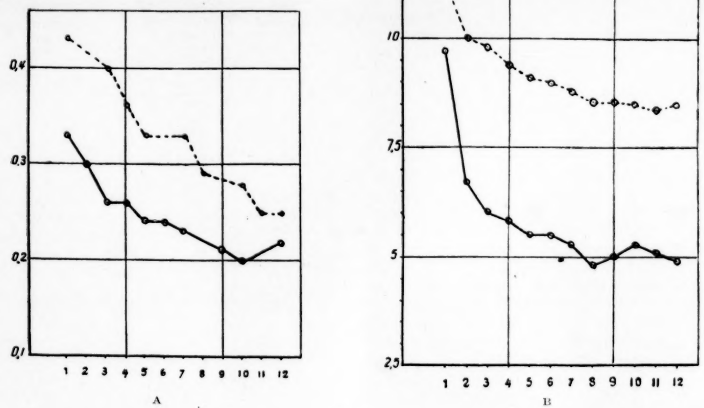

FIG. 4.

Average urinary excretion of A. Nitrogen and B. Creatinine of normal and hypophysectomized dogs (broken and solid lines respectively), during fasting.
Abscissae—Time of fasting in days.
Ordinates—A. Gm. N per Kgm. body weight per diem.
B. Mgm. Creatinine per Kgm. body weight per diem.

This lowered consumption of endogenous proteins is seen particularly and in a marked form in hypophysectomized animals suffering from pancreatic diabetes,[56-60] phlorhizin diabetes,[56-62] (table 5) or avitaminosis B and also after the injection of coli vaccine.[15-21]

In all these cases, and also in simple or protein fasting, the loss of weight of the hypophysectomized animals is on an average less than of the controls. They are also able to survive longer if they are not killed by a concurrent attack of hypoglycemia.

The lowered protein catabolism cannot be explained by hypothyroidism because, although thyroidectomized dogs have a decreased nitrogen excretion in simple or protein fasting, when there is need of large protein destruction (e.g., in pancreatic or phlorhizin diabetes) this is as exaggerated as in the controls, whereas the increase is very small in hypophysectomized animals. In the latter the formation of sugar at the expense of protein during diabetes is extremely diminished.

The change in the endogenous protein metabolism cannot be due to the simple operative trauma or to a superficial lesion of the tuber, since it is not observed in craniotomized animals or in those without the posterior lobe or with injury of the tuber (galvanocauterization of 3-5 mm. in depth and width, from the pituitary stalk to behind the mammillary bodies).

Implantation of the principal pituitary lobe causes an increase in the nitrogen excretion in fasting hypophysectomized toads.[22] Injection of thyrotropic extract of the anterior pituitary lobe causes an increase in the nitrogen excretion of normal or hypophysectomized rats during protein fasting for the first few days (Braier and Morea, unpublished) and slightly increases the protein catabolism in dogs.[66] We have not yet verified the duration of this action or whether it occurs by way of the thyroid.

The metabolism of nucleoproteins has been studied by Braier[22, 23] in hypophysectomized dogs and by Braier and Morea (unpublished data) in hypophysectomized rats.* In both species the hypophysectomized animals eliminate less uric acid and purin bases but more allantoin, whether on ordinary diet or protein fasting. But the total sum of the three quantities is equal to that in the controls. (Table 6.)

*According to Falta and Nowaczynski[325] in seven out of eight acromegalics there was an increase in the endogenous uric acid cf. [206 268 388 420] Schittenhelm and Harpuder[388] found a normal blood uric acid.

PLASMA PROTEINS AND NONPROTEIN NITROGEN

In the plasma of twelve hypophysectomized dogs, Goldberg[37] found an increase in the globulins (54 per cent) and in the viscosity (inconstant), but a decrease in the albumins (22 per cent) and in the A:G ratio (from 1.79 to 1.01). These modifications are identical with those seen in hypothyroidism.

Alkaline anterior pituitary extract, given intraperitoneally, produces not only a diabetic state, but also a marked increase in the total proteins, globulins, albumins and viscosity of the blood.[37] Immediately after injection of the extract there is a decrease in the nonprotein N which lasts several hours. (Braier, confirming Teel and Watkins.[419])

PHOSPHOCREATIN

When asthenia is well developed in the hypophysectomized toad (or in the toad after removal of only the glandular lobe) the phosphocreatin phosphorus in muscle diminishes in 33 per cent of the cases. The injection of glandular lobe extract or of mammalian anterior lobe extract brings it back to normal values.[104, 105]

TABLE 4

URINARY CREATININE IN MGM. PER KGM. PER DIEM

	Hypophysectomized	Lesion of Tuber Cinereum	Normals	Per Cent of Decrease of Hypophysectomized Animals Compared with Normals
DOGS				
Meat Diet				
Braier, 1931	23.5	31	28.7	—19
Braier, 1931	14.4	—	19.1	—24
Total Fasting				
10 days Braier, 1931	5.9	9.5	9.3	—35
2nd day Braier, 1931	11.7	—	15.6	—24
3rd day, with B. coli vaccine Braier, 1931	15.0	—	21.1	—29
Nitrogen Free Diet				
4th day Braier, 1931	6.1	—	10.0	—39
Minimum protein balance, with fat and starch diet Braier, 1931	7.0	—	11.1	—37
RATS				
Complete Diet				
Braier, Morea, 1935	25.7	—	29.1	—11
Nitrogen Free Diet				
Braier, Morea, 1935	12.7	—	18.0	—29

TABLE 5

AVERAGE URINARY NITROGEN IN DOGS UNDER DIFFERENT EXPERIMENTAL CONDITIONS FOR EACH GROUP

(Recorded in Gm. N per Kgm. Body Weight per Diem)

	17 Dogs Hypophysectomized	5 Dogs Tuberal Lesion	4 Dogs Thyroidectomized	10 Dogs Control
Fasting without phlorhizin	0.25	0.36	0.25	0.36
Fasting with phlorhizin	0.36	0.66	0.63	0.80
Absolute increase	0.11	0.30	0.38	0.44
Percentage increase	44	83	152	122

DIFFERENT DIETS PLUS PHLORHIZIN

Meat-Fed		*Sugar-Fed*		*Fat-Fed*	
4 Hypophysectomized	4 Control	4 Hypophysectomized	4 Control	4 Hypophysectomized	4 Control
1.37	1.56	0.30	0.76	0.33	0.73

GLUTATHIONE

Helen Maveroff,[114] in nine hypophysectomized dogs, found an average decrease of 10 per cent in the glutathione of the red blood cells (88 mgm. per cent as compared with 98 mgm. per cent in the controls). Injection of anterior lobe extract increases the glutathione in the red blood

cells of normal, hypophysectomized and thyroidectomized dogs.[114*]

In the hypophysectomized toads (or after removal of the glandular lobe) when the asthenia is evident, the glutathione decreases in the muscles and more markedly in the liver; implantation of the glandular lobe prevents this decrease.[104-111]

UROBILINURIA

Hypophysectomized dogs eliminate 0.12 mgm. per day of urobilin in the urine (average of fifty determinations in six dogs). This is a normal amount (Royer, unpublished data). Injection of 2 mgm. per Kg. tetrabromosulphthalein in these animals is followed by a blood curve of normal aspect (Royer, unpublished data).

TABLE 6

URINARY EXCRETION OF URIC ACID, PURINE BASES AND ALLANTOIN

(Recorded in Mgm. per Kgm. Body Weight per Diem)

	Uric Acid	Puric Bases	Allantoin
DOGS (Braier, 1933)			
Meat Diet			
Normals	4.5	12.8	40.7
Hypophysectomized	2.1	4.0	53.6
Nitrogen Free Diet			
Normals	2.0	4.3	16.6
Hypophysectomized	1.0	1.9	2.27
RATS (Braier and Morea, Unpublished)			
Complete Diet			
Normals	3.5	14.2	83
Hypophysectomized	2.5	14.0	92
Nitrogen Free Diet			
Normals	1.5	7.5	28
Hypophysectomized	0.9	5.2	35

URINARY EXCRETION OF PHOSPHORUS IN FASTING DOGS (GERSCHMAN, 1931)

(Recorded in Mgm. per Kgm. Body Weight per Diem)

	Meat Diet	Total Fasting	Nitrogen Free Diet
Normals	46.5	17.7	15.1
Hypophysectomized	42.9	13.7	6.7

INDOXYLEMIA

This is normal in hypophysectomized and in thyroidectomized dogs.[92]

PHENOLURIA

Hypophysectomized dogs eliminate normal amounts of urinary phenol, when on a meat diet, but the excretion diminishes in fasting and more especially in protein fasting.[34, 35, 104, 105]

FAT METABOLISM

Adiposity is a symptom of pituitary insufficiency in some species, but not in others. It forms part of the adiposogenital syndrome in man, due to lesion of the hypophysis or of the tuberal region. On the other hand in pituitary cachexia (Simmonds' syndrome) there is extreme emaciation. In hypophysectomized tadpoles the adipose organ persists.[406] Adiposity is frequently observed after hypophysectomy in puppies, but occurs rarely in the adult dog. It is almost constantly seen, and in extremely accentuated form, in dogs surviving tuberal lesions for a few months. (Solari,[133] confirming Camus and Roussy.) In the rat, adiposity is absent or may appear for a short time in a slight degree. Sooner or later these animals lose weight and become cachectic. (Morea, confirming Smith 1927-30.)

In hypophysectomized dogs there are slight variations in the total fats, fatty acids, and cholesterol of the blood, with a tendency toward a decrease.[118, 119, 120*] Munoz has seen that repeated injections of a diabetogenic anterior pituitary extract produce a marked increase in the total lipids of the blood (which has a milky aspect), as also in the fatty acids, cholesterol and phospholipids.† This can be observed in dogs of both sexes, castrates, thyroidectomized and after section of both splanchnic nerves and extirpation of the lumbar sympathetic chain. Extracts of kidney and muscle prepared by the same technique do not have this activity. The liver in these animals also has a fatty aspect.

Dogs showing manifest adiposity owing to tuberal lesions have a normal specific dynamic action. (Solari. [133])

Raab has proposed a theory which has been favorably received.[160, 270, 356, 363, 393] He believes that pituitrin and lipoitrin (which is found in both lobes of the pituitary and in the wall of the third ventricle) stimulate the tuber, from whence impulses travel by the spinal cord and the splanchnic nerves to the liver, increasing the fats in this organ and in the blood, owing to an increased mobilization of storage fat and consumption by the liver. A disturbance of some part of this complicated mechanism would cause an increase in fat storage and consequently adiposity. Munoz[120] could not find any activity tending to decrease the blood lipids in posterior pituitary extracts, in spite of having injected as much as 100 mgm. per Kg. of standard powder into dogs.

*Hidekazu[206] observed a decrease in the glutathione of hypophysectomized dogs and that prolan increased it.

*Karlik and Robinson[287] found hiperlipemia.

†This increase in lipids is mentioned by Baumann and Marine,[154] E. I. Evans,[221] etc.

KETONEMIA AND KETONURIA

Hypophysectomy considerably diminishes ketonuria; to 60 per cent of the normal in dogs under basal conditions;[129] to 28 per cent of that of the control animals in pancreatic diabetes;[128]† and to as low as 7 per cent of that of the control animals in phlorhizin diabetes during fasting.[128]‡ (Table 7.) Tuberal lesions also produce a small decrease in ketonuria in pancreatectomized dogs.

In hypophysectomized dogs on meat, sugar or fat diets the ketone elimination in phlorhizin diabetes is always smaller than in the corresponding controls. Sugar intake diminishes the elimination of ketones in the controls, but in the hypophysectomized there is a slight rise. Thyroidectomy, extirpation of the posterior lobe and lesions of the tuber do not diminish ketonuria as hypophysectomy does.[128]

The ketonuric activity of the anterior pituitary extract found in the rat by Burn and Ling,[139, 159, 172, 173, 209, 226, 236, 237, 238] has been studied in the dog by Rietti.[129] The total extract produces ketonuria in normal animals and this is more marked in partially pancreatectomized and hypophyso-pancreatectomized dogs.[66, 69, 70] In thyroidectomized dogs there was no significant increase but the ketonuric activity of the extract was not altered by castration, extirpation of the adrenal medulla, lesion of the tuber or section of the splanchnic nerves with extirpation of the lumbar sympathetic chain.[129] (Table 7.) In hypophysectomized phlorhizinized dogs the extract raises the excretion of ketones to the same level as in the controls.

†Long and Lukens[233] confirmed this in the cat.
‡Black[128] confirmed this in the rat.

TABLE 7

URINARY KETONE BODIES (VAN SLYKE, 1917), IN DOGS UNDER DIFFERENT EXPERIMENTAL CONDITIONS (RIETTI, 1932-34)

(Recorded in Mgm. per Kgm. Body Weight per Diem)

	6 Pancreatectomized Dogs	9 Pancreatectomized and Hypophysectomized Dogs	5 Pancreatectomized Dogs with Lesion of the Tuber Cinereum
	76	21	31

	6 Phlorhizin Dogs	6 Hypophysectomized Dogs Plus Phlorhizin	7 Dogs with Lesion of Tuber Cinereum Plus Phlorhizin	6 Thyroidectomized Dogs Plus Phlorhizin	4 Dogs without Posterior Lobe Plus Phlorhizin
Fasting	88	5	120	123	116
Meat 300 Gm.	56	12	—	—	—
Sugar 50 Gm.	35	18	—	—	—
Oil 100 Gm.	75	11	—	—	—

	Normals	Partial Pancreatectomized	Thyroidectomized	Castrated	Splanchnics Severed	Lesions of Tuber Cinereum	Without Adrenal Medulla
Without extract	6.2	8.5	5.8	3.8	4.5	10	4
With extract of glandular lobe of hypophysis	22.8	55	6.3	10.4	13.0	45	16

The increase in ketonemia produced by the anterior pituitary extract discovered by Anselmino and Hoffmann[137] has been repeatedly confirmed.[137, 138, 139, 162, 219, 238, 246, 258, 259, 272, 310, 338, 339, 340, 360, 393, 402, 403, 414, etc.]

The ketogenic extract has been called the "fat metabolism hormone" by Anselmino and Hoffmann and "Orophysin" by Magistris, names that are not suitable and should not be used because they presuppose something which is not yet proved. According to Anselmino and Hoffmann,[137 (cf. 246, 393)] after a fatty meal the blood contains this hormone in quantities sufficient to produce effects when injected into another rat. This substance is not identical with the glycogen mobilizing one[338, 339] nor with the thyrotropic hormone.[139, 159]

Urine has a ketogenic and ketonuric activity.[236, 237, 238, 239] Methods have been described for the extraction and purification of this substance, both from the urine and the pitui-

tary.[137, 138, 139, 237, 338] In thyroidectomized animals the ketogenetic activity is less than in normals according to Funk,[236] or almost completely absent according to Eitel, Löhr, and Loeser,[219] and Rietti.[129] Other workers, however, find that it may be normal.[159] Prolonged administration of the ketogenic substance produces the appearance of an antihormone in the serum.[158, 159]

It is surprising with what assurance some investigators explain the numerous metabolic effects of the pituitary or even all of its influence on the fat metabolism by the action of a single ketogenic hormone. Evidently the anterior lobe of the hypophysis participates in the regulation of the daily amount of urinary excretion of ketone bodies; however it has not been definitely established whether its rôle consists in increasing their production or decreasing their consumption.

CARBOHYDRATE METABOLISM*

BY BERNARDO A. HOUSSAY, M.D.

INTRODUCTION

DURING the last few years the important rôle which the pituitary plays in carbohydrate metabolism has been demonstrated. The essential physiological mechanism involves the anterior lobe, the posterior lobe having an accessory and much less important action. This is contrary to what has previously been supposed. The anterior pituitary lobe is probably, after the liver and pancreas, the most important regulator of carbohydrate metabolism. It would, however, be a grave mistake to imagine that the only metabolic function of the anterior pituitary is its action on carbohydrates. It holds a central position in the general metabolic regulation (water, iodine, protein, carbohydrate, fat, ketogenesis, etc.), as well as having essential and important actions on the endocrine system.

The alterations in the carbohydrate metabolism are especially marked in the toad, which is therefore the animal par excellence for its study. The changes appear or become accentuated about three weeks after hypophysectomy or extirpation of the principal lobe alone. At the same time symptoms of progressive neuromuscular asthenia develop, together with decrease in blood sugar and glycogen which causes death in four to eight weeks, survival for months being exceptional. Implantation of the principal lobe corrects these changes and prevents death. Similar symptoms are observed in hypophysectomized rats when they become cachectic. In dogs the compensation apparently is better, for they can survive for months or years in an apparently good state. However, they may present mortal cachexias or hypoglycemias. Despite their good appearance their metabolism is modified, as may be demonstrated by subjecting them to agents that induce hypoglycemia, or by producing diabetes, either by extirpation of the pancreas or by the administration of phlorhizin; these modifications affect particularly the metabolism of fasting animals.

Lesions of the tuber cinereum or of the hypothalamus have a varying effect on the pituitary functions, according to the localization and extent of the lesion. In certain cases they cause marked inhibition of the anterior pituitary function which may be corrected by administration of the anterior pituitary lobe.

*See footnote *, page 961.

THE BLOOD SUGAR IN HYPOPHYSECTOMIZED ANIMALS

Normal Blood Sugar. Many investigators have found subnormal blood sugar in hypophysectomized animals, dogs,[126, 279, 290, 293, 294, 333] rabbits,[191, 235] and in the pituitary cachexia of human beings. In reality, if the animals are properly cared for and are kept on an adequate diet, it has been found that the blood sugar remains within normal limits,* in dogs[15-21, 47-50, 85, 86, 88, 287] rabbits,[298, 379, 380] cats,[337] rats,[362] and amphibians.[29, 78, 93, 94, 401, 437]

However, one of the most salient characteristics of pituitary insufficiency is the tendency to hypoglycemia during fasting, which becomes manifest after a few hours.

Hypoglycemias. Hypophysectomized animals readily become hypoglycemic and may present grave symptoms, frequently terminating in death. Treatment with sugar produces spectacular improvement but must be initiated early and repeated frequently. Good results from injection of adrenalin or postpituitary extracts are much rarer.

The hypoglycemias may be classified according to their cause as postoperative, spontaneous, due to fasting, cachexia, insulin, phlorhizin, secondary, etc. After operation[252, 268, 342, 431] or during the evolution of pituitary cachexia [146, 174, 251, 257, 325, 326, 327, 361, 366, 379, 380, 404, 432] hypoglycemia and hypoglycemic crises frequently occur. "Spontaneous" hypoglycemia, observed first by Wilder[432] in man and by Houssay and Biasotti [56-60] in dogs, has since been seen in dogs,[56-60, 187, 200, 290] rabbits,[191, 431] guinea

*In 20 hypophysectomized dogs we found 0.097 per cent in the morning and 0.1 per cent 2½ hours after a meat meal; in 20 controls the figures were 0.105 per cent and 0.109 per cent respectively.

pigs[222] and rats. The surprising feature is that it may develop in hypophysectomized dogs which are also pancreatectomized.[56-60] We have never seen spontaneous hypoglycemia in dogs with extensive lesions of the tuber (retropituitary), but D'Amour and Keller[200] have observed it with lesions in other parts of the brain.

Fasting is the essential factor in the rapid, progressive decrease of the blood sugar, which, if not treated, may produce serious or even fatal accidents. This has been proved principally by Braier[14-21] and has been confirmed in the dog,[15-21, 58, 187, 200, 325-334] rabbit,[191, 431] and monkey.[187] While the blood sugar level is low there is little glycogen in the liver in dogs (Houssay, unpublished) and rabbits.[191]

Phlorhizin produces a rapid hypoglycemia in the fasting dog[56-62] and in the toad,[28] accompanied by convulsions and death. These accidents usually appear in the dog on the third day, when the blood sugar is below 70 mgm. per cent. Under these conditions we lost fifteen out of seventeen hypophysectomized dogs. Feeding meat and sugar prevents the hypoglycemia and the consequent accidents, but feeding fat is not efficacious.[13] Treatment with a diabetogenic anterior pituitary extract, before and during fasting, prevents the occurrence of hypoglycemia and death.[48, 49, 50, 66]

Secondary hypoglycemias are observed after epinephrin;[14-21, 325] and glucose[325] hyperglycemias; and may be serious if they occur after fasting.

Sensitivity to Insulin. Another remarkable peculiarity of pituitary insufficiency is the extreme sensitivity to the toxic and blood sugar reducing actions of insulin, which even in small doses produces convulsions, coma and frequently death. In hypophysectomized animals the fall in blood sugar is more rapid, more marked and lasts longer than in the normal, and recuperation is difficult and slow if it takes place at all. Early, intense and repeated treatment with cane sugar, glucose or posterior pituitary extract is necessary, and is frequently efficacious in the dog. This extreme sensitivity to insulin, which we found with Magenta in 1924 has been proved in dogs,[85, 86, 87, 148, 149, 199, 216, 241, 242, 279, 293, 325, 332, 333, etc.] cats,[337] toads,[93, 95] monkeys,[260] rabbits,[190, 191, 235, 297, 298, 379, 380, 381] and man [141, 262, 257, 327, 335, 349, 366, etc.] but apparently is not present in birds.[268] It is also seen in hypophysectomized dogs from which the pancreas as well has been removed.*

The protective action of anterior lobe extract is very potent, and is incomparably superior to that of the posterior lobe extract. It is able to correct the sensitivity to insulin and even to produce a supernormal resistance. This occurs in both normal and hypophysectomized toads,[95] dogs[29, 332] and rabbits.[190] Injections of anterior pituitary extract for one to two days are needed to reinforce the resistance[29] since such injections are unable to save animals already in convulsions or coma.[87]

A number of observations have been made on the relation of the thyroid to the hypersensitivity to insulin. The protective action of anterior pituitary extract is also evident in hypophysectomized-thyroidectomized animals. (di Benedetto, Houssay.) The hypersensitivity of hypophysectomized dogs is much greater than that of thyroidectomized dogs. Thyroidectomized rabbits[190] and thyroidectomized dogs (Houssay) become far more sensitive to insulin when they are later hypophysectomized. Thus it is clear that the decrease in resistance to insulin is not due to hypothyroidism in the hypophysectomized animals but to the lack of the anterior pituitary lobe.

It has been thought that the hypersensitivity to insulin is due to hypofunction of the adrenals,[152] because extirpation of the latter produces a similar hypersensitivity, as shown by Lewis and Magenta in our Institute. Furthermore, in pituitary insufficiency there is often an atrophy of the adrenal cortex. In opposition to this view we cite the following observations: Anterior pituitary extract has a diabetogenic action on hypophysectomized-pancreatectomized toads from which the adrenals also have been removed, and on dogs after extirpation of the adrenal medulla or after complete adrenalectomy.[84, 101] It also increases the resistance of the latter to insulin. According to Barnes, Dix and Rogoff[148] hypophysectomized dogs require more adrenalin to prevent convulsions than dogs with denervated adrenals. These authors maintain that hypophysectomized animals do not liberate adrenalin during the hypoglycemia due to insulin. Cope and Marks[190] showed, however, that there was a hypersecretion of adrenalin, and they advanced the idea that the glycogenolytic action of adrenalin is less marked in the absence of the anterior pituitary lobe.

Our opinion is that pituitary insufficiency causes the suppression of a hormone which is necessary for the metabolism of carbohydrates, and that it is the lack of this hormone which causes hypersensitivity to insulin. Adrenal insufficiency may be an additional cause.

Hypoglycemic action of the blood. Cowley[192] stated that the blood of hypophysectomized animals produces hypoglycemia in rabbits but this was found in only one case out of three by Daggs and Eaton[199] and could not be confirmed by di Benedetto[30] using the blood of sixteen hypophysectomized dogs.

Képinov and Guillaumie[291] using a pancreatojugular anastomosis have found that the pancreatic blood of hypophysectomized dogs is more

*Unpublished data. See also 187 and 367.

hypoglycemic than that of the controls; the pituitary would retard the secretion of insulin and extirpation of the pituitary exaggerate it. Recently the same authors have shown that stimulation of the peripheral end of the vagus causes a marked hypoglycemia in hypophysectomized animals whether the adrenal veins are intact or not.

UTILIZATION OF SUGAR IN PITUITARY INSUFFICIENCY

Respiratory Quotient. Hypophysectomized dogs apparently do not have a raised consumption of sugar, since their basal metabolism is slightly diminished and the R. Q. is normal.[1, 2, 3, 4, 48, 53, 54, 55, 117, 240] If they are given glucose the R. Q. rises as in the controls.[9, 10, 11, 12, 59]

Glycogen. The hepatic glycogen was found normal in hypophysectomized dogs by Aschner,[140] but we found an average of 2.7 per cent in seven hypophysectomized dogs and 3.48 per cent in six controls without anesthetic, and 1.63 per per cent in four hypophysectomized and 2.1 per cent in nine controls under chloralose. In the rabbit the hepatic glycogen has been found to be low,[298, 351] or normal with decrease during fasting.[191] In the hypophysectomized toad it falls gradually, especially from the third week when the asthenia appears.[75, 78, 93, 94, 401] The muscle glycogen does not change in rabbits[351] or dogs (our Institute) and decreases slowly in toads.[75, 78, 93, 94, 401*] After tetanization it is resynthesized in hypophysectomized dogs as completely as in controls. (Dambrosi, 1933.) The *cardiac glycogen* is found to be less than normal when bradycardia occurs in hypophysectomized toads.[123]

It is possible that the velocity of the formation and decomposition of glycogen is altered. Phillips and Robb[362] observed that hypophysectomized rats form much less hepatic glycogen and somewhat less muscle glycogen when given glucose than do the controls. According to Fluch, Greiner and Loewi[228] the liver of hypophysectomized frogs perfused with Ringer's solution, either alone or adrenalinized, gives up less glucose than the liver of normal frogs. It is still doubtful whether the pituitary plays any rôle in the accumulation of glycogen which occurs in the *thesaurosis glycogenica* of Gierke.[226, 264, 327]

Blood sugar curves. Cushing and his collaborators[245] found that larger doses of sugar by mouth or glucose by injection were necessary to produce glycosuria in hypophysectomized than in normal dogs.† This increase in tolerance was confirmed by Karlik and Robinson[287] but was not present in the dogs studied by Camus and Roussy[179] and only occurred in some of those studied by Houssay, Hug and Malamud.[83]

If hypophysectomized rabbits receive glucose by mouth the blood sugar rises less and the secondary fall in blood sugar is greater than in normal rabbits.[191, 235, 379, 380, 381] Lucke, Heydemann, and Hechler,[332] in one incompletely hypophysectomized dog found a greater absolute increase and a marked secondary drop. Other investigators[9-12, 200, 292] have found the blood sugar curve to be more prolonged in hypophysectomized dogs. The velocity of absorption has not been studied in either species although in hypophysectomized rats Phillips and Robb[362] found it was slower than was normally the case.

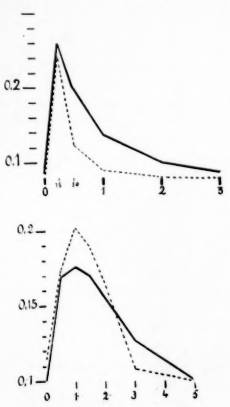

FIG. 5.

A. Blood sugar in 10 normal (broken lines) and 14 hypophysectomized dogs (solid lines) following 1 Gm. of glucose per Kg. body weight intravenously.

B. Blood sugar in 5 normal (broken lines) and 7 hypophysectomized dogs (solid lines). Two Gm. glucose per Kg. body weight per os.

Abcissae—Time in hours after glucose administration.
Ordinates—Blood sugar in Gm. per 100 cc. blood.

In the dog no modification of tolerance is demonstrable by continuous intravenous injection of glucose[83, 143, 188] but in rabbits, five hours after extirpation of the pituitary, there is a larger consumption.[252] When only one intravenous dose is given, the curve of hyperglycemia shows a slower fall in hypophysectomized dogs than in the controls.[10, 199, 216] (Fig. 5.) Képinov[289, 290] found a rapid rise with abrupt and intense fall, but perhaps this better assimilation was due to other factors, such as the general condition of his dogs. In the toad *Xenopus laevis*, injection of sugar causes a greater rise in blood sugar with better tolerance after hypophysectomy than before.[437]

*Muscle lactic acid is normal in these animals in the resting condition, but after tetanus it increases less than in the controls.[131]

†It is observed in hypophysectomized animals with an Eck fistula.[291]

HYPERGLYCEMIAS IN HYPOPHYSECTOMIZED ANIMALS

Adrenalin[191, 235, 297, 381] or pilocarpin[298] hyperglycemia is less marked in hypophysectomized rabbits than in normals and grave secondary hypoglycemias usually follow. Similarly, hypophysectomized toads have a lower hyperglycemia after adrenalin and morphine injections.[75] Parathormone does not cause a rise in blood sugar in hypophysectomized pigeons.[370] The hyperglycemia of avitaminosis[19] fails to occur in hypophysectomized dogs while that caused by ether is less intense than in normal controls.[31] The hyperglycemias due to glycocol,[126] thyroxin[279, 228, 330] and pituitrin[279, 293] are somewhat greater. The morphine hyperglycemia is similar in hypophysectomized and in normal dogs.[31]

Adrenalin subcutaneously does not usually produce glycosuria in hypophysectomized dogs as it does in the controls.[39, 140] The blood sugar rise has been found both greater[293, 325, 326, 327, 332, 333] and less[16, 279] after hypophysectomy. Braier observed that after eighteen hours' fasting the rise is slightly less in the hypophysectomized dogs than in the controls. After four days of fasting there is still less hyperglycemia and a marked secondary fall in blood sugar (six out of ten of the dogs dying in hypoglycemia).

PANCREATIC DIABETES IN HYPOPHYSECTOMIZED ANIMALS

Hypophysectomy brings about a marked alleviation of the symptoms of pancreatic diabetes, resulting in a less intense and slower development of that disease. The hypophysectomy is equally efficient if it is performed before or after the pancreatectomy. This alleviation of pancreatic diabetes, which we proved with Biasotti and described in 1929-30,[45, 58*] has been amply confirmed in dogs,[58, 59, 113, 128, 129, 147, 149, 158, 186, 187, 286, 289, 290, 299, 329, 367, 409] cats,[204, 205, 322, 323] amphibians,[6, 22, 23, 25, 56-65, 84*] reptiles (*Ophis merremi* Wagler[63, 64, 65]), fishes (*Mustelus canis*[359]).

Hypophysectomized toads and toads in which the principal lobe alone has been extirpated do not have glycosuria and there is little or no hyperglycemia, nor is the urinary nitrogen excretion raised, on removal of the pancreas. On the other hand, diabetes appears with normal, or even supernormal, intensity if the principal lobe is implanted (the neuro-intermediate lobe is less active). (Table 8.)

We have studied sixty-five hypophysectomized-pancreatectomized animals. On the basis of this material it may be stated that the usual syndrome of pancreatic diabetes in mammals undergoes numerous changes due to the hypophysectomy. As compared with control cases of pancreatic diabetes in otherwise normal animals, the hypophysectomized-pancreatectomized animals show the following characteristics. Survival is prolonged and may reach six,[58] or even nine months.[147, 187] The wounds heal and there are fewer infections. The loss of weight occurs more slowly. Glycosuria diminishes and sometimes is not present, and fasting causes a more marked decrease. Polyuria is scarce or absent, depending on the degree of glycosuria. The blood sugar in general is lower, oscillating between 0.1 and 0.25 per cent. (Table 9.) Sometimes there is no hyperglycemia and it is even possible for hypoglycemic crises which improve on administration of sugar to occur. Together with this there is hypersensitivity to insulin.[149, 187] The ketones in the blood and urine decrease markedly, but the alkaline reserve falls slightly or not at all, although the calcium in the blood is lowered.† There is a small increase

*Goetsch, Cushing and Jacobson[245] had previously observed that subtotal hypophysectomy may increase glucose tolerance in dogs with a subtotal pancreatectomy in experiments which were repeated by Cushing[103] and Davidoff and Cushing.[203]

*In the species *Bufo arenarum*, *B. marinus*, *B. paracnemis*, *B. d'Orbigny*, *Ceratophrys ornata*, *Leptodactylus ocellatus*.

†With lesions of the parathyroids; but it is also observed when pancreatectomy alone is performed.[113]

TABLE 8

BLOOD SUGAR IN GM. PER 100 CC.

Toads *Bufo arenarum* Hensell

Averages

	Normals	Cranio-tomized	Hypophysectomized	Without Glandular Lobe	Tuber Cinereum Lesion
With pancreas	0.064	0.064	0.051	0.056	0.057
Implantation of glandular lobe	0.068	0.069	0.058	0.069	0.060
Pancreatectomized	0.199	0.169	0.094	0.094	0.117
Pancreatectomized with implantation of glandular lobe	0.256	0.278	0.228	0.214	0.234
Pancreatectomized with implantation of neuro-intermediate lobe	—	—	0.110	—	—

TABLE 9

No.	Survival After Second Operation, Days	Weight, Kgm. Initial	Weight, Kgm. Final	Averages: Urine, cc. Per Day	Glucose Eliminated, Gm. Per Day	Glucose Eliminated, Gm. Per Kgm. Per Day	N. Eliminated, Gm. Per Day	N. Eliminated, Gm. Per Kgm. Per Day	D:N	Glycemia Average Gm. %	Interval Between Operations, Days
				Dogs Without Pituitary and Without Pancreas							
1	180	8.6	6.4	868	21.60	3.23	14.70	2.15	1.61	0.250	39
27	154	12.8	5.1	274	9.83	1.30	7.81	1.05	1.23	0.287	24
36	90	8.5	6.3	211	5.16	0.72	5.76	0.80	0.88	0.136	240
35	64	13.4	6.9	221	6.30	0.69	8.92	0.99	0.70	0.238	55
38	51	10.3	5.4	166	7.21	0.76	3.89	0.43	1.85	0.325	210
23	41	9.8	6.1	164	1.97	0.25	.....	.....	.....	0.267	27
11	35	12.4	10.2	356	0.688	0.059	.....	.....	.....	0.113	61
15	28	10.5	7.4	253	3.15	0.895	.....	.....	.....	0.218	41
29	25	10.0	6.1	160	4.42	0.552	.....	.....	.....	0.275	30
				Pancreatectomized Dogs With Lesion of the Tuber							
64	10	8.7	6.4	513	21.26	2.95	8.18	1.13	2.60	0.327	35
77	10	7.5	5.2	456	18.96	3.05	7.10	1.14	2.67	0.345	30
85	9	8.0	6.4	267	12.13	1.75	4.16	0.60	2.91	0.310	29
86	9	6.2	4.1	273	11.97	2.60	4.57	0.99	2.61	0.298	30
				Pancreatectomized and Thyroidectomized Dogs							
1	24	8.1	4.7	373	.....	3.18	.....	1.61	2.37	0.293	.....
2	21	8.6	6.2	360	.....	3.10	.....	1.27	2.05	0.326	.....
5	9	15.5	12.8	626	.....	2.55	.....	0.95	2.72	0.370	.....
3	9	10.2	8.5	268	.....	1.47	.....	0.59	1.92	0.366	.....
4	7	11.0	8.6	423	.....	2.15	.....	.....	.....	0.435	.....
				Pancreatectomized Dogs							
	7 to 30	up to 50% loss		500 to 2000	.....	2 to 4	.....	0.7 to 1.8	2.8	0.3 to 0.4	

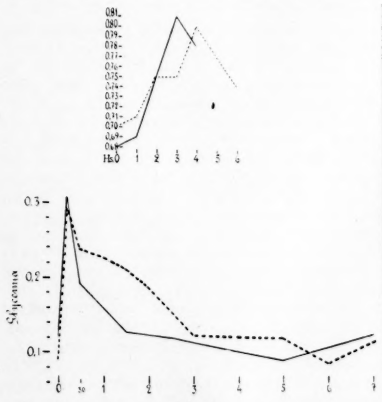

FIG. 6.

A. R. Q. following the intravenous administration of 1 Gm. of glucose in the hypophysectomized dog No. 159, before (solid line) and after pancreatectomy (broken line).
Abscissae—Time in hours after injection.
Ordinates—R. Q.

B. Blood sugar after administration of glucose to the hypophysectomized dog No. 9, before (solid line) and after pancreatectomy (broken line).
Abscissae—Time in hours after administration of glucose.
Ordinates—Concentration of blood sugar in Gm. per 100 cc. blood.

in the catabolism of proteins (slight and slow loss of weight, slightly increased nitrogen elimination during fasting). The dextrose-nitrogen ratio is low. The lipids and cholesterol in the blood rise less than in the controls.[119, 120] The hepatic and muscular glycogen may be found in normal quantities,[63, 64, 65, 187] although following tetanization the restitution of muscle glycogen may not occur until after an hour.[27] If sugar is administered, the animals can partially or even sometimes totally utilize it;[12, 60] the respiratory quotient rises, occasionally as much as in normal animals.[12, 59, 149] (Fig. 6.) The hyperglycemic curve falls more rapidly than in animals with pancreatic diabetes, although more slowly than in normals. Repeated administration of sugar aggravates the diabetic state.

This proves clearly that even without the internal secretion of the pancreas the organism can utilize sugar. In pancreatic diabetes it seems that the secretion of the anterior pituitary increases the production of glucose and diminishes its consumption so that the organism becomes overcharged with sugar.

The work of Képinov[289] is in favor of this hypothesis of ours. This investigator found that transfusion of the blood of pancreatectomized dogs into normals caused a secondary net rise of blood sugar (independently of the sugar injected) which did not occur if the blood of

pancreatectomized-hypophysectomized animals was used.

According to Boller, Uiberrak and Falta[164] if the blood of healthy individuals injected with insulin is transfused into normals it causes a lowering of the blood sugar of the recipient. If, however, the donor is an insulin resistant subject injected with insulin, hypoglycemia is not produced in the recipient. The blood of insulin resistant individuals seems to contain one or more antagonistic bodies.

Folliculin. X-Rays. — It has been possible to modify pancreatic diabetes by inhibition of the pituitary in other ways. With treatment by folliculin the pancreatic diabetes of dogs[149, 151, 352, 353] and monkeys[352, 353] has been prevented or improved and its development retarded; human cases of diabetes have also been improved in this way.[348*]

On the other hand, unpublished observations of Biasotti indicate that irradiation of the pituitary, before or after pancreatectomy, gives no results. (cf. 398) It is, however, uncertain whether the pituitary is affected by this treatment. This method has been tried in human diabetes.[214, 234, 373, etc.]

PANCREATIC DIABETES OF THYROIDECTOMIZED AND ADRENALECTOMIZED ANIMALS

Thyroidectomy does not alleviate pancreatic diabetes in dogs.[435] If in a pancreatectomized dog all adrenal tissue is extirpated and the administration of insulin is suspended, there is a marked rise in blood sugar which may remain at a high level or may decline.[145, 247, 261, 311, 316] Dogs with no adrenal medulla have an intense pancreatic diabetes.[276, 311, 415, 423] Thus it is clear that the adrenal is not indispensable for the rise in blood sugar to the diabetic level, nor is the adrenin from the adrenal necessary for its maintenance.†

With unilateral adrenalectomy we did not find any modification of the pancreatic diabetes; although Barnes, Scott, Ferrill and Rogoff[152] observed this. Long and Lukens[322, 323] found that adrenalectomized-pancreatectomized cats, maintained with cortin, presented an attenuated diabetes with little or no hyperglycemia, glycosuria or ketonuria. Both groups of investigators think that possibly hypophysectomy causes alleviation of the diabetes because it provokes an adrenal hypofunction.

DIABETES AND HYPOTHALAMIC LESIONS

In a certain number of dogs and cats[39, 83, 140, 155, 179, 180, 183, 232, 243, 255, 264, etc.] a transient glycosuria is noted after hypophysectomy. This is not due to the glandular deficiency because it is observed after mere manipulation of the hypophysis without extirpation[179, 180, 245, etc.] and after lesions of the tuber cinereum.[39-47, 140, 144, 180, 201, 204, 207, 313, 314, 346, 378, etc.] It has also been noted that hypothalamic excitation may cause a rise in blood sugar.[270, 280, 341, 350]

The glycosuric action of excitation of the superior cervical sympathetic ganglion has been attributed to a pituitary hyperfunction, but this has not been confirmed.[168, 288, 365] The fact that it ceases on section of the splanchnics and on bilateral lesion of the hypothalamus[204] suggests the possibility that there is a central reflex which acts through the liver or the adrenal.[277, 282]

Lesions of the nuclei in the wall of the third ventricle sometimes produce glycosuria in the rabbit.[177, 305] Dewulf,[210, 211] however, could not confirm this by making lesions in these nuclei, although when there were other mesencephalodiencephalic lesions, excluding the tuber, glycosuria did occur. It is as well to mention that both investigators observed some cases of spontaneous glycosuria. We ourselves have never observed a permanent hyperglycemia or glycosuria in dogs with either circumscribed or extensive lesions of the diencephalon. On the other hand, certain hypothalamic lesions may cause hypoglycemic crises.[200] Although lesions of the diencephalon and of other central zones have been observed in some cases of diabetes[215, 307, 308, 309, 312, 314, 345, 347, 355, 399, 425, etc.] they are usually absent.[210, 305]

Certain lesions of the tuber may inhibit the pituitary diabetogenic secretion since Houssay and Biasotti[56, 60] found that following such lesions there was a marked decrease in the pancreatic diabetes of toads,* but that implantation of the glandular lobe resulted in its reappearance. The pituitary of these toads contained diabetogenic substances, but apparently could not secrete it. Our dogs with tuberal lesions extending from the pituitary stalk to behind the mammillary bodies, developed a pancreatic diabetes as severe as that of the controls.[58†] However, after more extensive hypothalamic lesions (caudo-dorso-lateral to the mammillary bodies, in the region of the ventromedial nucleus of the hypothalamus) pancreatectomy did not produce a high blood sugar and life was prolonged in both dogs and monkeys.[204, 205] Anterior pituitary extract aggravates this attenuated diabetes. Davis's opinion, quoted from a letter, coincides with ours and is "that we have simply produced a functionless pituitary gland by interference with its blood and nerve supply with the lesion in the hypothalamus, which must be very accurately placed".

*Biasotti (unpublished) observed a remarkable case in a child.

†The relationship of the adrenals to diabetes is considered in detail, with a very complete bibliography, by my pupil Leloir.[311]

*In the fish *Mustelus canis* after the tuberal lesion was produced there was a slight increase in the pancreatic hyperglycemia.

†The glycemic curves following injection of glucose in dogs with tuberal lesions are similar to those seen in normal controls.[9 10 11 12]

PHLORHIZIN DIABETES OF HYPOPHYSECTOMIZED ANIMALS

Hypophysectomy causes a decrease in the intensity of phlorhizin diabetes* in fasting dogs[48, 49, 50, 56-62] (table 10) and toads,[28] but the blood sugar falls rapidly, death occurring in from two to seven days (fifteen out of seventeen dogs). The glycosuria, ketonuria,[128, 129] urinary nitrogen, dextrose-nitrogen ratio and loss in weight, are all diminished. (Table 10.) On a meat or sugar diet, hypoglycemia and death do not occur, but on a fat diet they do. In all cases less sugar is excreted by the hypophysectomized animals than by the controls. Tuberal lesions or previous thyroidectomy do not affect the phlorhizin glycosuria.

TABLE 10

AVERAGES. DOGS UNDER PHLORHIZIN (5-7 DAYS). BLOOD SUGAR MGM. PER 100 CC.

	Hypophysectomized		Tuberal Lesions		Without Posterior Lobe		Thyroidectomized		Controls	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Fasting	98	67	104	88	87	77	108	87	113	104
Meat fed	102	93	—	—	—	—	—	—	101	92
Sugar fed	94	86	—	—	—	—	—	—	105	105
Fat fed	88	56	—	—	—	—	—	—	112	120

AVERAGES. URINARY GLUCOSE ELIMINATED IN GM. PER KGM. PER DIEM

Fasting	0.68	1.54	2.31	1.91	2.00
Meat fed	3.30	—	—	—	4.22
Sugar fed	2.56	—	—	—	4.23
Fat fed	0.82	—	—	—	2.55

ACTION OF PITUITARY EXTRACTS ON THE BLOOD SUGAR

Extract of the posterior pituitary lobe raises the amount of sugar in the blood. Extracts with three different actions can be obtained from the anterior lobe, (a) with hypoglycemic action, (b) with slight, quick, transitory hyperglycemic action due to intervention of the adrenals, and (c) with diabetogenic action.

Hyperglycemic action of posterior lobe extracts.—Since Borchardt[165] found that posterior lobe extracts produced glycosuria, this phenomenon, together with the hyperglycemia, has been the object of numerous studies.† We have shown[76, 77] that the hyperglycemic action is slight and increases with the dose; and that the vasopressor substance has the more intense action. It does not develop if the liver or adrenals are extirpated, but if the pancreas alone has been removed it is normal and there is very little increase after section of the vagi. The action is on the liver, with particiipation of the normal adrenal secretion. It has not been possible to demonstrate an increase in the secretion of adrenalin. Foglia[32] could not confirm the direct stimulation of the pancreas found by La Barre, although the latter used adrenalectomized dogs while those of Foglia had intact adrenals.

Posterior lobe extract, even in repeated large doses, does not produce diabetes in normal dogs[45-50, 427] or in dogs with incomplete removal of the pancreas[69, 70] but causes a slight rise in the blood sugar of hypophysectomized animals with no pancreas. The neuro-intermediate lobe in the toad (corresponding to the posterior lobe of mammals) has similar metabolic actions to those of the principal lobe, although less intense. It counteracts the toxic and hypoglycemic actions of insulin,[95*] increases the diabetes of hypophysectomized - pancreatectomized toads,[37] counteracts the asthenia and lengthens the life of hypophysectomized toads† and causes an increase in their diminished glycogen content.[48, 49, 50]

Hypoglycemic action of the anterior lobe.—Certain anterior pituitary lobe extracts produce hypoglycemia.[138, 273, 339, 340, 409, 436, etc.] According to Anselmino and his collaborators they have a pancreatotropic action since they cause hypertrophy of the islets of Langerhans in the rat‡ and do not produce hypoglycemia in pancreatectomized dogs. The increase in the secretion of insulin was proved by Zunz and La Barre,[436] using a panereaticojugular anastomosis. The pancreatotropic hormone is active in thyroidectomized animals; it decreases alimentary and adrenalinic hyperglycemias and lowers the glycogen content of the muscles. Its preparation and properties have been studied in detail by Anselmino and his collaborators.

The rapid and transient hyperglycemic action of anterior lobe extracts and of urine.—The commercial extract (of unknown preparation)

*Aschner performed a few experiments.

†This work has been summarized by Houssay[41] and Houssay and di Benedetto.[76 77 78]

*The fact that it also has an antagonistic function in the dog has been mentioned above. (See under sensitivity to insulin in hypophysectomized dogs.[42 44 45 56 87 105] etc.)

†The activity in this respect is considerably less than that of the anterior lobe, and is destroyed by boiling for five minutes.

‡Anselmino very kindly sent me his histological preparations.

used by Lucke and his collaborators caused an immediate rise in blood sugar of not more than 30 to 50 mgm. per cent which lasted for a few hours. This action is produced through the sympathico-adrenal path and is absent in adrenalectomized animals and in those with section of the splanchnics or under the influence of ergotamine or somnifen. It has a rapid action if injected into the cerebrospinal fluid.† This immediate action has also been found in other extracts.[274, 400]

Extracts of normal urine or pregnancy urine contain hyperglycemic substances[63, 64, 65, 163, 206, 217, 258, etc.] which can also be found in the ketogenetic extracts prepared from them.[258, 402, 403] These do not invariably alter the blood sugar nor do the following: purified prolan,[206, 213, 327, 408, etc.] the galactotropic substances,[354] the thyrotropic substances,[327, 330] nor various other pituitary extracts.[278] The action of the urine is due to the urie or hippuric acid according to Davis, Hinsey and Markee.[206]

Glycogenolytic action.—The hepatic glycogen decreases after injection of various extracts of anterior pituitary lobe.[139, 274, 284, 327, 433, etc.] The ketogenetic[402, 403, 414, etc.] and especially the thyrotropic[218, 219, 319, 389] extracts have this effect.

According to Anselmino and Hoffmann[139] the anterior pituitary contains a glycogenolytic substance (on which they have bestowed the rather unfortunate name of Kohlehydratstoffwechselhormon) which is secreted into the blood. After a carbohydrate meal the blood, if removed and injected into a rat, has the power of diminishing the hepatic glycogen. In fasting, the blood does not have this power except in diabetics. The blood of hypophysectomized dogs does not acquire the glycogenolytic capacity after carbohydrate intake. Hoffmann and Anselmino[273] describe the properties of the hormone and its separation from the ketogenic substances.

Glycogenetic action.—According to Magistris[338, 339, 340] certain extracts of anterior pituitary lobe allow glycogen to be formed in the livers of rats in hyperthyroidism when sugar has been administered.

DIABETOGENIC ACTION OF ANTERIOR PITUITARY LOBE EXTRACT

Amphibians. — In hypophysectomized-pancreatectomized amphibians, particularly the toad, glandular lobe extract of amphibians, birds, fishes and mammals[63, 64, 65] produces diabetogenic effects which are more intense than those produced by the intermedio-neural or posterior lobe extract. Anterior lobe raises the blood sugar of normal toads only slightly but produces a considerable increase in the diabetes of hypophysectomized-pancreatectomized animals, with hyperglycemia, glycosuria[56, 60, 61, 62, 64] (table 8) and an increase in urinary nitrogen.[22] This diabetogenic action does not occur if the liver is absent[25] although the muscular glycogen falls less than in the untreated hepatectomized controls. The diabetogenic action is observed in hypophysectomized-pancreatectomized animals even if the thyroids or testes, digestive tract, kidney or adrenals, diencephalon and anterior cerebrum are absent.[56,60]

In hypophysectomized toads, extracts of this lobe cause an improvement of the asthenia and a lengthening of the survival time;[48, 49, 50] there is a rise of glycogen[78] and of lactic acid formation during tetanic stimulation of the muscles.[106] It also causes an increase in the glycosuria following phlorhizin[28] and in the hyperglycemias following adrenalin and morphine injection.[75]

Normal mammals.—The hyperglycemic and glycosuric actions of anterior lobe extract have been described by Johns, O'Mulvenny, Potts and Laughton.[284*] The diabetogenic action has been observed and studied minutely by Evans,† Houssay,[9-12, 29, 48, 49, 50, 63-66, 69, 70, 71, 74] Baumann and Marine,[154] Barnes and Regan,[149] and E. I. Evans.[221] It is the only glandular extract known at present which will produce a definite diabetic state,‡ since extracts of liver, muscle, thyroid, spleen, kidney, testicle, posterior pituitary lobe, and adrenalin all either have no action on the blood sugar or increase it only slightly.

In the dog the blood sugar gradually rises from the second or third day of injection until it reaches levels of 0.18 to 0.30 per cent (on carbohydrate diet the rise occurs more rapidly and is more intense). (Fig. 7.) After two days and before hyperglycemia develops there is considerable increase in the resistance to the toxic action of insulin (both in normal and hypophysectomized animals) even if the thyroids or adrenal medulla are removed.[29, 190, 327]

The hyperglycemias due to adrenalin and morphine are also increased.[76, 77]

Besides the hyperglycemia there is glycosuria, ketonuria,[129§] increase in plasma proteins,[37] increase in hematic glutathione,[114] hyperlipemia and hypercholesterolemia,[120, 154, 221] acidosis,[221] etc. During the hyperglycemia there is diminished glucose tolerance (fig. 8) since the hyperglycemia curve falls gently and approximates the diabetic one.[9, 10, 11, 12, 149, 221] The respiratory quotient does not rise and part of the injected

†We found the action of this extract to be very weak, even repeated high doses did not increase the glycemia more than 30 mg. per cent transitorily and showed no diabetogenic action.

*They do not give their method of preparation of the extract, but they say it is protein-free (which seems impossible to us), and their glycemias are not over 0.150 per cent.

†Evans, Meyer, Simpson, Reichert[222 224] produced diabetes which persisted for a few weeks after the treatment had been discontinued.

‡The extract should be prepared from fresh, frozen anterior lobes and kept at a low temperature.

§It is also seen after extirpation of the gonads or section of the splanchnics, etc., but not after thyroidectomy.

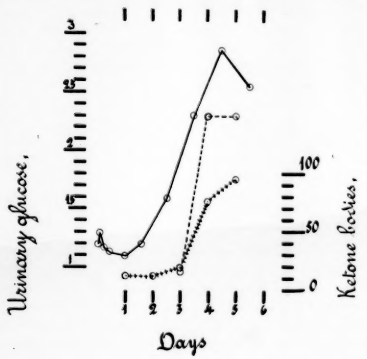

FIG. 7.

Normal dog No. 2, daily injection 6 cc. (1.2 Gm.) per Kgm. body weight of anterior lobe extract.

— — — Urinary glucose, Gm. per Kgm. per diem.
——— Blood sugar in Gm. per 1000 cc. blood.
+ + + Urinary Ketone bodies, mgm. per Kgm. per diem.

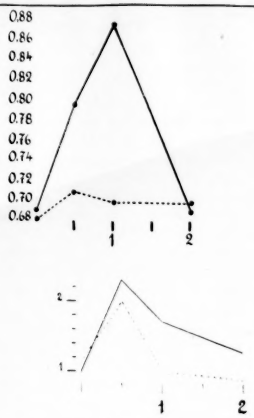

FIG. 8.

A. R. Q. in the normal dog No. 2 following the intravenous injection of 1 Gm. of glucose before (solid line) and after (broken line) treatment with anterior lobe extract.
Abscissae—Time in hours after injection.
Ordinates—R. Q.

B. Blood sugar in the normal dog No. 4 following the intravenous injection of 1 Gm. glucose per Kgm. body weight before (broken line) and after (solid line) treatment with anterior lobe extract.
Abscissae—Time in hours after injection.
Ordinates—Blood sugar concentration in Gm. per 1000 cc. blood.

sugar is eliminated.[9, 10, 11, 12] It is worthy of note that during the intense hyperglycemia there is an increase in glycogen.[74] (Table 11.)

This action is observed in various species† and can be obtained in castrated or thyroidectomized dogs and in those with no adrenal medulla, with lesions of the tuber, or with section of the splanchnics and extirpation of the lumbar sympathetics.[71] If dogs deprived of one adrenal are injected with anterior lobe extract and when in hyperglycemia the second adrenal is removed, but with the injections still continued, the blood sugar remains high or falls gently during two or more days, whereas there is a rapid fall if the injection of extract is suspended when the second adrenalectomy is performed. (Fig. 9.) For this reason and also be-

†In order of decreasing activity: cats, dogs, pigeons, guinea pigs, rabbits, rats, mice; it was not obtained in toads and snakes.

TABLE 11

GLYCOGEN PER 100 GM. BEFORE AND 2 HOURS AFTER INTRAVENOUS INJECTION OF 1 GM. OF GLUCOSE PER KGM. BODY WEIGHT

Chloralose Anesthesia	Liver Glycogen in Gm.		Muscle Glycogen in Mgm.	
	Before	2 Hour	Before	2 Hour
9 Normal dogs	2.10	2.65	528	583
6 Dogs injected 6 days with anterior lobe extract, glycemia above 0.18%	2.73	2.84	515	615
4 Dogs with splanchnic nerves severed, injected 6 days with anterior lobe extract	3.30	3.40	665	734
7 Dogs injected 6 days with anterior lobe extract. No diabetes	1.90	2.36	434	560
8 Thyroidectomized dogs	2.16	2.48	512	609
10 Thyroidectomized dogs injected 6 days with anterior lobe extract	2.62	3.05	493	528
4 Hypophysectomized dogs (1)	1.63	1.94	—	—
3 Hypophysectomized dogs injected 6 days with glandular lobe extract	2.63	3.01	555	595
4 Pancreatectomized dogs	1.45	1.78	340	337
10 Hypophysectomized and pancreatectomized dogs	2.32	3.04	528	580

(1) The chloralose anesthesia has an unfavorable influence on the hypophysectomized dogs. Without anesthesia:—2.77 Gm. % in the liver and 510 mgm. % in the muscle (averages of 7 hypophysectomized dogs); 3.48% in the liver and 539 mgms. in the muscle (average of 6 normals). (Houssay, Biasotti, unpublished data.)

cause the diabetogenic action can be obtained in hypophysectomized-pancreatectomized and adrenalectomized toads, it is evident that this pituitary extract has its own action which is independent of the adrenals.*

The diabetes produced by the anterior pituitary lobe extract has five marked characteristics: (1) it generally does not occur until the second or third day; (2) it does not occur or is hardly evident during fasting; (3) if administration of the extract is suspended the blood sugar falls rapidly and reaches a normal level in one to three days; (4) it is accompanied by a rise in glycogen (this is the only diabetes in

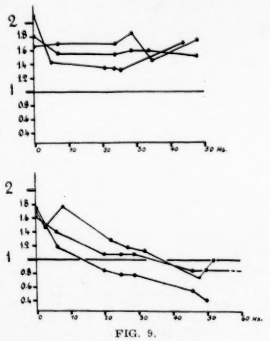

FIG. 9.

Blood sugar in dogs. In all cases one adrenal was removed and anterior lobe extract injected until the blood sugar rose above 1.6 Gm. per 1000 cc. The remaining adrenal was then removed.

The injections of anterior lobe extract were continued in the cases shown in graph A, but were stopped in those shown in graph B.

Abscissae—Time in hours after complete adrenalectomy.
Ordinates—Blood sugar in Gm. per 1000 cc. blood.

which this occurs); (5) the diabetes occurs even if the thyroids and suprarenals are absent.

If the injections are continued the blood sugar may fall to normal levels,[221, 400] which gives rise to the theory that there may be an antihormone,[186] however, it must be remembered that diabetes has still been observed after several months of uninterrupted treatment.[223, 224]

Action in the pancreatic diabetes of hypophysectomized animals.—When there is subtotal pancreatectomy (with or without glycosuria) the diabetogenic action is particularly intense. If there is total pancreatectomy all the symptoms of diabetes are intensified, especially the ketosis, and death occurs in one to three days.

In hypophysectomized - pancreatectomized mammals the anterior pituitary lobe extract causes an increase in the diabetes. The hyperglycemia, ketonuria, glycosuria, etc., reach abnormally high figures. These effects occur in the same manner whether the thyroid or gonads are extirpated or not.

Action in phlorhizin diabetes.—In the toad[28] and particularly in the dog[65, 66] anterior pituitary extract causes an aggravation of phlorhizin diabetes in hypophysectomized animals; it doubles the glycosuria, causes an immense increase in the ketonuria, accelerates the fall in weight, and increases the diuresis, but prevents the hypoglycemia and rapid death.

NAME, PROPERTIES AND ACTION OF THE SUBSTANCE WHICH IS ACTIVE ON CARBOHYDRATE METABOLISM

Of the substances present in the anterior pituitary secretion, the blood sugar lowering agent has been demonstrated pharmacologically but not physiologically. We do not yet know the importance of the glycogenolytic agent (the Kohlehydratstoffwechselhormon of Anselmino and Hoffmann). It can, however, be taken as proved that there is an anterior pituitary secretion which maintains the normal blood sugar, prevents the occurrence of hypoglycemia and raises the blood sugar in diabetes.

One may speak of the diabetogenic action of the extracts but it is not advisable to say there is a definite diabetogenic hormone, since its normal physiological action cannot be to produce diabetes. It seems that its action is to stimulate and facilitate the production of sugar and perhaps regulate its utilization; in large doses it produces hyperglycemia and diminishes sugar consumption. It would be more satisfactory to call it the glucose regulating (or glucido-regulating) hormone of the anterior pituitary.

Although in general it has antagonistic actions to those of insulin, it should not be called a contra-insular hormone (Lucke) because (1) it acts in hypophysectomized-pancreatectomized animals and its rôle is not exclusively anti-insulinie; (2) many other hormones (viz., adrenalin, posterior pituitary, etc.) are anti-insulinic. It has a direct action, not through its influence on the thyroids or adrenals, although it is clear that its effectiveness, like that of other agents, is less or may even fail in profound adrenal insufficiency.

The chemical properties of the glucose-regulating hormone are not completely known although we[56-61] have studied them in the toad and the ox.[71, 325, 326, 327] It is soluble in water, partially so in alcohol at 50-60°; insoluble in acetone, absolute alcohol, ether, methyl alcohol, chloroform, benzine; partially precipitated by 95 per cent alcohol, acetone, and 30 per cent Na_2SO_4 (anhydrous). It is destroyed rapidly by heating above 55° to 80° C. It is absorbed by charcoal or kaolin and in great part by the filters. It is not ultrafiltrable or dialyzable. It is distinct from the gonadotropic, thyrotropic and mammotropic hormones but cannot be separated from the growth hormone.

*In contradistinction to what has been maintained by Lucke[325, 326, 327] perhaps because his extracts had little activity or were of another kind.

PITUITARY AND LACTIC ACID

Marenzi's work[106-111] has shown that there is an increase in the lactic acid of the blood due to the action of posterior pituitary lobe extract and during the diabetic action of anterior pituitary lobe. The lactic acid is normal in the blood of hypophysectomized animals, and is also normal in the muscles of resting hypophysectomized toads (or of those with extirpation of the posterior lobe). After several weeks, however, tetanization causes a smaller increase of lactic acid as compared with the normals, probably because the initial content of glycogen is diminished.

CARBOHYDRATE METABOLISM IN DISEASES OF THE HUMAN PITUITARY

It has already been mentioned that in serious pituitary insufficiency there is hypoglycemia with hypoglycemic crises and hypersensitivity to insulin. Hyperglycemia due to glucose or adrenalin may be less[361] or greater than in normals[325, 326, 327] but is frequently followed by profound secondary hypoglycemia.

Glycosuria is very frequent in cases of Cushing's syndrome (it was found in nine out of twenty-three cases in which basophile adenoma of the pituitary was histologically confirmed). There may be hyperglycemia with prolonged glycemic curves.[267] The insulinic hypoglycemia curve is normal[267] or lower[349] but without hypoglycemic symptoms.

Glycosuria and hyperglycemia are frequent in acromegaly, there is a diminished fall in blood sugar due to insulin, and the alimentary glycemia curves are prolonged,[203, 217, 301, 327, 343, 358, 361, etc.

(3) Anterior pituitary extract can produce diabetes in normal mammals.

(4) When the pituitary is absent there is a tendency to hypoglycemia, hypersensitivity to insulin and other hypoglycemic agents, etc.

In acromegaly, glycosuria is frequent (table 12), and occasionally it is even possible for a diabetic state to develop, with irregularities, fluctuations or remissions. In 32 per cent of six hundred and fifty cases reviewed by Atkinson[142] glycosuria was mentioned. That this glycosuria or diabetes is due to hyperfunction of the anterior pituitary seems probable on the basis of various arguments formulated by Davidoff and Cushing:[203] (1) in these cases there is always an acidophile adenoma of the anterior pituitary; (2) diabetes usually does not occur in cases of chromophobe adenomas or other pituitary lesions;* (3) pancreatic lesions are not constant in such cases; (4) partial extirpation of the tumors causes an improvement; (5) some of these cases are insulin resistant;† (6) extirpation or irradiation of the pituitary lowers this resistance.

The histological changes in the pituitary in cases of diabetes have been studied with contradictory results and interpretations.[156, 157, 196, 212, 233, 295, 304, 392, 395, 429] It is probable that there is a pituitary factor in all cases of diabetes to a greater or lesser extent, for example it is possible that it has a more important influence in cases of infantile diabetes, etc.

SUMMARY OF THE METABOLIC ACTIONS OF THE PITUITARY

The anterior pituitary has a tonic action on the basal metabolism since it develops and maintains the thyroids.

TABLE 12

FREQUENCY OF GLYCOSURIA IN ACROMEGALY

	Cases with Glycosuria	Total No. of Cases of Acromegaly	%
1. Hansemann, D.: Berl. klin. Wchnschr. 34:417, 1897.	12	97	12
2. Hinsdale, G.: Acromegaly. Medicine 4:442, 1898.	14	130	10
3. Borchardt, L.: Ztschr. f. klin. Med. 66:332, 1908.	71	176	49
4. Rosenberger, F.: Die Ursachen der Glykurie. Muenchen. 1911.	82	196	42
5. Davidoff, L. M., and Cushing, H.: Arch. Int. Med. 39:751 (June) 1927.	25	100	25
6. Atkinson: Acromegaly. Bale. London. 1932.	208	650	32

THE PITUITARY AND DIABETES*

Our experimental work has shown:

(1) In the absence of the pituitary (or of the anterior lobe) pancreatic and phlorhizin diabetes is attenuated and animals retain and consume glucose.

(2) Anterior pituitary lobe extract counteracts the action of insulin, increases pancreatic and phlorhizin diabetes, etc.

*We have published papers on this subject in 1930-31-34.

The neuro-intermediate lobe regulates the secretion of water by the kidney (in amphibians and perhaps in mammals).

The anterior pituitary, by its action on the thyroids and perhaps partly through other mechanisms, influences the concentration of iodine in the blood.

*Colwell[138] collected 38 cases; Davidoff and Cushing[203] found it in 4 out of 168 of their cases, etc.

†Resistance to insulin in acromegaly has been found to be increased,[203 256 325 327 349 424] normal[103 158 227 265 302 303 304 361 378 394 424] or decreased.[242]

It maintains the potassium in the plasma at a normal level.

It stimulates the endogenous protein catabolism and the protein minimum, particularly in fasting, diabetes, etc.

It has some influence on the nucleoprotein metabolism (stimulation of production of uric acid).

It has an action on the protein equilibrium of the plasma (through the thyroid).

It has a definite stimulatory action on ketonuria.

Its action on the deposition and consumption of fats varies from species to species.

In the absence of the anterior pituitary there is a great decrease in the excretion of sugar during fasting in diabetes and the new formation of sugar from protein is diminished.

Hypophysectomized animals readily become hypoglycemic and may present grave symptoms and frequently die. Treatment with sugar produces spectacular improvements.

Diabetes in hypophysectomized animals is less intense and they are able to utilize sugar. Excess of anterior pituitary lobe aggravates the diabetes or produces it in normal animals, and causes a hyperglycemia which results in a poor consumption of glucose. It considerably increases the resistance to insulin in normal and hypophysectomized dogs. It has a direct action which is seen in the absence of the pancreas, gonads, thyroid or adrenals, etc.

In pituitary insufficiency of the dog there does not appear to be an excessive consumption of glucose (low basal metabolism, normal respiratory quotient and glycogen). However, only a very careful study of the consumption of sugar in different animal species would definitely establish whether it is normal, increased or decreased. For fasting animals glycogen is low.

Without doubt the pituitary is one of the most important metabolic regulatory organs and in some species (in the toad particularly) it is of vital necessity. In the future it will be impossible to study any metabolic problem, whether normal or pathologic, without reference to the pituitary. Growth, endocrine regulation (including the reproductive functions) and metabolic regulation form the functional trinity of the anterior pituitary gland.

REFERENCES

1. Artundo, A.: Cong. Intern. Biol. Montevideo. (Oct.) 1930; Arch. Soc. Biol. Montevideo, 1931. Supl. fasc. **2**:288; Rev. Soc. argent. de biol. **6**:497, 1930; Compt. rend. Soc. de biol. **106**:137 (Jan.) 1931.
2. Artundo, A.: Cong. Intern. Biol. Montevideo. (Oct.) 1930; Arch. Soc. Biol. Montevideo, 1931. Supl. fasc. **2**:296; Rev. Soc. argent. de biol. **6**:507, 1930; Compt. rend. Soc. de biol. **106**:139 (Jan.) 1931.
3. Artundo, A., Mazzocco, P.: Rev. Soc. argent. de biol. **6**:391, 1930; Cong. Intern. Biol. Montevideo. (Oct.) 1930; Arch. Soc. Biol. Montevideo, 1931. Supl. fasc. **2**:301; Compt. rend. Soc. de biol. **105**:713 (Dec. 12) 1930.
4. Artundo, A., Solari, L. A.: Rev. Soc. argent de biol. **9**:143 (June) 1933; Compt. rend. Soc. de biol. **114**:385, 1933.
5. Biasotti, A.: Rev. Circ. Méd. Argent. y Centro Est. Med. **22**:1979, 1922; Segundo Cong. Nac. Med. (Bs. As.) **4**:911 (Oct.) 1922; Compt. rend. Soc. de biol. **88**:361, 1923.
6. Biasotti, A.: Semana méd. **1**:1251 (May 15) 1930.
7. Biasotti, A.: La Prensa Méd. Argent. **20**:1234, 1932.
8. Biasotti, A.: Rev. Soc. argent. de biol. **9**:499 (Nov.) 1933; Compt. rend. Soc. de biol. **115**:329, 1934.
9. Biasotti, A.: Rev. Soc. argent. de biol. **10**:36 (April) 1934; Compt. rend. Soc. de biol. **116**:455, 1934.
10. Biasotti, A.: Rev. Soc. argent. de biol. **10**:124 (June) 1934; Compt. rend. Soc. de biol. **117**:54, 1934.
11. Biasotti, A.: Congr. Nac. Med. (Rosario) **3**:302, 1934.
12. Biasotti, A.: Rev. Soc. argent. de biol. **10**:82 (May) 1934; Compt rend. Soc. de biol. **116**:898, 1934.
13. Biasotti, A., and Houssay, B. A.: J. Physiol. **77**:81 (Dec.) 1932.
14. Braier, B.: Cong. Intern. Biol. Montevideo, 1931. Supl. fasc. **2**:304, 1931.
15. Braier, B.: Rev. Soc. argent. de biol. **6**:254, 1931; Compt. rend. Soc. de biol. **118**:128, 1931.
16. Braier, B.: Rev. Soc. argent. de biol. **7**:283, 1931; Compt. rend. de biol. **108**:491 (Oct. 30) 1931.
17. Braier, B.: Rev. Soc. argent. de biol. **7**:140, 1931; Compt. rend. Soc. de biol. **112**:1195, 1931.
18. Braier, B.: Rev. Soc. argent. de biol. **7**:305, 1931; Compt. rend. Soc. de biol. **108**:495, 1931.
19. Braier, B.: Rev. Soc. argent. de biol. **7**:323, 1931; Compt. rend. Soc. de biol. **108**:507 (Oct. 30) 1931.
20. Braier, B. Rev. Soc. argent. de biol. **7**:340, 1031; Compt. rend. Soc. de biol. **108**:508, 1931.
21. Braier, B.: Tesis Doct. Farm. y Bioquim. 1931; An. Farm. Bioquim. **3**:24, 61, 97, 1931.
22. Braier, B.: Rev. Soc. argent. de biol. **9**:72 (May) 1933; Compt. rend. Soc. de biol. **114**:80, 1933.
23. Braier, B.: Rev. Soc. argent. de biol. **9**:365 (Oct.) 1933; Compt. rend. Soc. de biol. **114**:1209, 1933.
24. Braier, B., and Morea, R.: Rev. Soc. argent. de biol. **11**:38 (April) 1935; Compt rend. Soc. de biol. **119**:881, 1935.
25. Campos, C. A.; Curutchet, J. L., and Lanari, A.: Rev. Soc. argent. de biol. **9**:11 (April) 1933; Compt. rend. Soc. de biol. **113**:467, 1933.
26. del Castillo, E. B., and Calatroni, C.: Rev. Soc. argent. de biol. **5**:250, 1929; Compt. rend. Soc. de biol. **102**:455 (Nov. 8) 1929.
27. Dambrosi, R. G.: Tesis Doctorado Medicina. 1933. Rev. Soc. argent. de biol. **15**:344, 1934.
28. di Benedetto, E.: Rev. Soc. argent. de biol. **7**:196, 1931; Compt. rend. Soc. de biol. **107**:1193 (July 16) 1931.
29. di Benedetto, E.: Rev. Soc. argent. de biol. **8**:578, 1932; Compt. rend. Soc. de biol. **112**:499 (Feb. 10) 1933.
30. di Benedetto, E.: Rev. Soc. argent. de biol. **10**:23 (April) 1934; Compt. rend. Soc. de biol. **116**:449, 1934.
31. di Benedetto de Sabelli El. and di Benedetto, E.: Rev. Soc. argent. de biol. 1935. In press.
32. Foglia, V. G.: Rev. Soc. argent. de biol. **7**:361, 1931; Compt. rend. Soc. de biol. **108**:500, 1931.
33. Galán, J. C.: Rev. Asoc. méd. argent. **32**:203, 1929; (Soc. Biol. **1**:57); Compt. rend. Soc. de biol. **83**:1357 (July 22) 1929.
34. Gerschman, R.: Rev. Soc. argent. de biol. **7**:302, 1931; Compt. rend. Soc. de biol. **108**:494 (Oct. 30) 1931.
35. Gerschman, R.: Rev. Soc. argent. de biol. **7**:350, 1931; Compt rend. Soc. de biol. **108**:501 (Oct.) 1931.
36. Gerschman, R., and Marenzi, A. D.: Rev. Soc. argent. de biol. 1935.
37. Goldberg, I.: Rev. Soc. argent. de biol. **8**:610 (Oct.-Nov.) 1932. V Congr. Nac. Med. Rosario. **3**:249, 1934.
38. Houssay, B. A.: Prensa med. argent. **2**:315, 1915; Endocrinol. **2**:94, 1918; Compt. rend. Soc. de biol. **81**:381, 1918.
39. Houssay, B. A.: Primer Cong. Nac. Med. Bs. Aires **4**:40, 1916.
40. Houssay, B. A.: Segundo Cong. Nac. Med. **4**:865, 1922.
41. Houssay, B. A.: Accion fisiologica de los extractos hipofisarios. 1918, 1922, 1a y 2a edic. 415 pág., Flaiban, edit., Bs. Aires.
42. Houssay, B. A.: Libro de homenaje al Prof. Dr. Luis Güemes, 1923; Rev. Mexicana Biol. 4, 1, 1923; Rev. Med. Barcelona **6**:328, 1926 (Soc. Biol. Barceiona [Nov.] 1924).
43. Houssay, B. A.: Presse méd. 1246, 1925.
44. Houssay, B. A.: Semana méd. **32**:189, 1925; Arch. Endocrin. Nutric. (Madrid) **3**:385, 1925; Endokrinol. **9**:456, 1925.
45. Houssay, B. A.: A Patol. Geral. 131, 1929; Bol. Acad. Nac. Med. Bs. As. 251, 1929; Libro de Oro en homenaje al Dr. Gregorio Araoz Alfaro 271, 1929; Endokrinol. **5**:103, 1929.
46. Houssay, B. A.: Arch. Soc. Biol. Montevideo **2**:199, 1930; Rev. Asoc. méd. argent. **43**:519, 1930; Presse méd. 237, 1931.
47. Houssay, B. A.: Hosp. argent. **2**:369, 1931; Rev. Franc. d'Endocrin. **9**:423, 1931; Klin. Wchnschr. 1529, 1932.
48. Houssay, B. A.: Bol. Acad. Nac. Med. 140, 1933; Endocrinol. **18**:409, 1934
49. Houssay, B. A.: Anales Fac. Med. Montevideo **18**:75, 1933; Vol. Jubilaire, Marinesco 301, 1933; Klin. Wchnschr. **12**:773 (May 20) 1933.
50. Houssay, B. A.: Rev. Soc. argent. de biol. **9**:34 (April) 1933; Compt. rend. Soc. de biol. **113**:472, 1933
51. Houssay, B. A.: Soc. Biol. Montevideo (Oct.) 1934 (100a sesion, en homenaje a los profesores Bottazzi y Houssay).
52. Houssay, B. A.: V Cong. Nac. Med. Rosario **3**:199, 1934.
53. Houssay, B. A., and Artundo, A.: Rev. Soc. argent. de biol. **9**:161 (June) 1933; Compt. rend. Soc. de biol. **114**:391, 1933.

54. Houssay, B. A., and Artundo, A.: Rev. Soc. argent. de biol. **9**:66 (May) 1933; Compt. rend. Soc. de biol. **114**:79, 1933.

55. Houssay, B. A., and Artundo, A.: Rev. Soc. argent. de biol. **9**:158 (June) 1933; Compt. rend. Soc. de biol. **114**:392, 1933.

56. Houssay, B. A., and Biasotti, A.: Arch. internat. de pharmacodyn. et de thérapie **38**:250, 1930.

57. Houssay, B. A., and Biasotti, A.: Rev. Soc. argent. de biol. **6**:326, 1930; Compt. rend. Soc. de biol. **105**:126, 1930; Pflügers Archiv. Physiol. **227**:657, 1931.

58. Houssay, B. A., and Biasotti, A.: Rev. Soc. argent. de biol. **6**:251, 1930; Compt. rend. Soc. de biol. **105**:121 (Oct. 16) 1930; Pflügers Archiv. Physiol. **227**:664, 1931.

59. Houssay, B. A., and Biasotti, A.: Actas Cong. Intern. Biol. Montevideo (Oct.) 1930; Arch. Soc. Biol. Montevideo, 1931; Supl. fasc. **2**:277; Bol. Acad. Nac. Med. 457, 1930; Endocrinol. **15**:511, 1931.

60. Houssay, B. A., and Biasotti, A.: Rev. Soc. argent. de biol. **6**:48, 1930; Compt. rend. Soc. de biol. **104**:407, 1930; Pflügers Arch. Physiol. **227**:239, 1931.

61. Houssay, B. A., and Biasotti, A.: Rev. Soc. argent. de biol. **7**:2, 1931; Compt. rend. Soc. de biol. **107**:733 (July 19) 1931.

62. Houssay, B. A., and Biasotti, A.: Endocrinol. **15**:511, 1931.

63. Houssay, B. A., and Biasotti, A.: Rev. Soc. argent. de biol. **9**:29 (April) 1933; Compt. rend. Soc. de biol. **113**:469, 1933.

64. Houssay, B. A., and Biasotti, A.: Rev. Soc. argent. de biol. **9**:29 (April) 1933; Compt. rend. Soc. de biol. **113**:469, 1933.

65. Houssay, B. A., and Biasotti, A.: Bol. Acad. Nac. Med. 63, 1933.

66. Houssay, B. A.; Biasotti, A.; di Benedetto, E., and Rietti, C. T.: Rev. Soc. argent. de biol. **8**:563, 1932; Compt. rend. Soc. de biol. **112**:494 (Feb. 10) 1933.

67. Houssay, B. A.; Biasotti, A., and Mazzocco, P.: Compt. rend. Soc. de biol. **108**:914, 1931; Rev. Soc. argent. de biol. **7**:447, 1931

68. Houssay, B. A.; Biasotti, A., and Mazzocco, P.: Rev. Soc. argent. de biol. **8**:554 (Oct.-Nov.) 1932; Compt. rend. Soc. de biol. **113**:459, 1933.

69. Houssay, B. A.; Biasotti, A., and Rietti, C. T.: Rev. Soc. argent. de biol. **8**:469 (Aug.-Sept.) 1932; Compt. rend. Soc. de biol. **111**:479 (Nov. 4) 1932.

70. Houssay, B. A.; Biasotti, A., and Rietti, C. T.: Bol. Acad. Nac. Med. 171, 1932.

71. Houssay, B. A.; Biasotti, A., and Rietti, C. T.: Rev. Soc. argent. de biol. **9**:489 (Nov.) 1933; Compt. rend. Soc. de biol. **115**:323, 325, 327, 1934.

72. Houssay, B. A., and Carulla, J. E.: Rev. Asoc. méd. argent. **32**:51, 1920; Compt. rend. Soc. de biol. **83**:1252, 1920.

73. Houssay, B. A.; Carulla, J. E., and Romaña, L.: Rev. Asoc. méd. argent. **32**:41, 1920; Compt. rend. Soc. de biol. **83**:1250, 1920.

74. Houssay, B. A.; Deulofeu, V., and Marenzi, A. D.: Annual Rev. Bioch. **4**:279, 1935.

75. Houssay, B. A., and di Benedetto, E.: Rev. Soc. argent. de biol. **8**:448 (Aug.-Sept.) 1932; Compt. rend. Soc. de biol. **111**:472 (Nov. 4) 1932.

76. Houssay, B. A., and di Benedetto, E.: Rev. Soc. argent. de biol. **9**:78, 1933; Compt. rend. Soc. de biol. **114**:82, 1933.

77. Houssay, B. A., and di Benedetto, E.: Rev. Soc. argent. de biol. **9**:300, 310, 1933; Compt. rend. Soc. de biol. **114**:793, 1933.

78. Houssay, B. A.; di Benedetto, E., and Mazzocco, P.: Rev. Soc. argent. de biol. **9**:4, 1933; Compt. rend. Soc. de biol. **113**:465, 1933.

79. Houssay, B. A.; Galán, J. C., and Negrete, J.: Rev. Asoc. méd. argent. 32, 1920; Compt. rend. Soc. de biol. **83**:1248, 1920.

80. Houssay, B. A.; Giusti, L., and Goñalons, G. P.: Rev. Soc. argent. de biol. **1**:237, 1925; Compt. rend. Soc. de biol. **93**:969, 1925.

81. Houssay, B. A., and Hug, E.: Rev. Asoc. méd. argent. **34**:43, 1921 (Soc. Biol. **2**:113) Compt. rend. Soc. de biol. **85**:681, 1921.

82. Houssay, B. A., and Hug, E.: Rev. Asoc. méd. argent. **34**:136, 1921; (Soc. Biol. **2**:136) Compt. rend. Soc. de biol. **85**:815, 1921.

83. Houssay, B. A.; Hug, E., and Malamud, T.: Rev. Asoc. méd. argent. **34**:1128 (Nov.) 1921 (Soc. Biol. **2**:290); Compt. rend. Soc. de biol. **86**:1115, 1922.

84. Houssay, B. A., and Leloir, L. F.: Rev. Soc. argent. de biol. 1935; Compt. rend. Soc. de biol. 1935.

85. Houssay, B. A., and Magenta, M. A.: Rev. Asoc. méd. argent. **37**: (Soc. argent. de biol. **5**:389) 1924; Compt. rend. Soc. de biol. **92**:822, 1925.

86. Houssay, B. A., and Magenta, M. A.: Rev. Soc. argent. de biol. **3**:217, 1927; Compt. rend. Soc. de biol. **97**:596, 1927.

87. Houssay, B. A., and Magenta, M. A.: Rev. Soc. argent. de biol. **5**:99, 1929; Compt. rend. Soc. de biol. **102**:429, 1929.

88. Houssay, B. A., and Mazzocco, P.: Rev. Asoc. méd. argent. **34**:1165 (Nov.) 1921 (Soc. Biol. **2**:327); Compt. rend. Soc. de biol. **86**:409, 1922.

89. Houssay, B. A.; Mazzocco, P., and Biasotti, A.: Compt. rend. Soc. de biol. **108**:915 (Dec. 4) 1931; Rev. Soc. argent. de biol. **7**:450, 1931.

90. Houssay, B. A.; Mazzocco, P., and Biasotti, A.: Rev. Soc. argent. de biol. **8**:321, 1932; Compt. rend. Soc. de biol. **111**:401, 1932.

91. Houssay, B. A.; Mazzocco, P., and Biasotti, A.: Rev. Soc. argent. de biol. **8**:254, 1932; Compt. rend. Soc. de biol. **111**:82, 1932.

92. Houssay, B. A.; Mazzocco, P., and Potick, D.: Rev. Soc. argent. de biol. **10**:507, 1934; Compt. rend. Soc. de biol. **117**:1255, 1934.

93. Houssay, B. A.; Mazzocco, P., and Rietti, C. T.: Rev. Soc. argent. de biol. **1**:231, 1925; Compt rend. Soc. de biol. **93**:968, 1925.

94. Houssay, B. A.; Mazzocco, P., and Rietti, C. T.: Rev. Soc. argent. de biol. **1**:227, 1925; Compt. rend. Soc. de biol. **93**:967, 1925.

95. Houssay, B. A., and Potick, D.: Rev. Soc. argent. de biol. **5**:66, 1929; Compt. rend. Soc. de biol. **101**:940, 1929.

96. Houssay, B. A., and Rietti, C. T.: Rev. Soc. argent. de biol. **8**:53, 1932; Compt. rend Soc. de biol. **110**:144, 1932.

97. Houssay, B. A., and Rietti, C. T.: Rev. Soc. argent. de biol. **8**:249, 1932; Compt. rend. Soc. de biol. **111**:80, 1932.

98. Houssay, B. A., and Romaña, L.: Primer Cong. Nac. Med. **4**:69, 1916; La Prensa méd. argent. **4**:284, 1917.

99. Houssay, B. A., and Rubio, H.: Segundo Cong. Nac. Med. **4**:870, 1922; Compt. rend. Soc. de biol. **88**:358, 1923.

100. Hug, E.: Rev. Asoc. méd. argent. **34**:1124 (Soc. Biol. **2**:44) 1921; Compt. rend. Soc. de biol. **85**:594, 1921.

101. Leloir, L. F.: Tesis Fac. Med. Bs. As. 1934.

102. Magenta, M. A.: Rev. Soc. argent. de biol. **5**:89, 1929; Compt. rend. Soc. de biol. **102**:428, 1929.

103. Marenzi, A., and Biasotti, A.: Compt. rend. Soc. de biol. **89**:1125, 1923; Rev. Asoc. méd. argent. **36**:690, 1923 (Soc. Biol. **4**:192).

104. Marenzi, A. D.: Estudios bioquimicos sobre los fenoles. 1933. Bs. As. Palumbo ed.

105. Marenzi, A. D.: Rev. Soc. argent. de biol. **9**:43, 1933; Compt. rend. Soc. de biol. **114**:394, 1933; Cong. Nac. Med. Rosario **3**:269, 1934.

106. Marenzi, A. D.: V Cong. Nac. Med. Rosario **2**-9 Set. **3**:269, 1934.

107. Marenzi, A. D.: V Cong. Nac. Med. Rosario **3**:245, 1934.

108. Marenzi, A. D.: Rev. Soc. argent. de biol. **10**:121, 1934; Compt. rend. Soc. de biol. **117**:53, 1934.

109. Marenzi, A. D.: Rev. Soc. argent. de biol. **10**:173, 1934; Compt. rend. Soc. de biol. **117**:457, 1934; An. Farm. Bioquim. **5**:18, 1934.

110. Marenzi, A. D.: Rev. Soc. argent. de biol. **10**:250, 1934; Compt. rend. Soc. de biol. **117**:464, 1934.

111. Marenzi, A. D.: Rev. Soc. argent. de biol. **10**:290 (Sept.-Oct.) 1934; Compt. rend. Soc. de biol. **117**:1035, 1934.

112. Marenzi, A. D., and Gerschman, R.: Rev. Soc. argent. de biol. **10**:131 (June) 1934; Supl. fasc. **10**:350; Compt. rend. Soc. de biol. **117**:56, 1934.

113. Marenzi, A. D., and Gerschman, R.: Compt. rend. Soc. de biol. **118**:488, 1935.

114. Maveroff, H.: Rev. Soc. argent. de biol. **8**:614 (Oct.-Nov.) 1932.

115. Maveroff de Lissner, H.: Rev. Soc. argent. de biol. **9**:227, 1933; Compt. rend. Soc. de biol. **114**:726, 1933.

116. Mazzocco, P.: Rev. Soc. argent. de biol. **3**:213, 1927; Compt. rend. Soc. de biol. **97**:594, 1927.

117. Mazzocco, P.: Rev. Soc. argent. de biol. **8**:621 (Oct.-Nov.) 1932; Compt. rend. Soc. de biol. **113**:456, 1933.

118. Muñoz, J. M.: Tesis Doct. Med. Bs. As. 1931.

119. Muñoz, J. M.: Rev. Soc. argent. de biol. **8**:587, 1932; Compt. rend. Soc. de biol. **112**:502 (Feb. 10) 1933.

120. Muñoz, J. M.: Actas y trab. del quinto Cong. nac. de med. **3**:242, 1934.

121. Novelli, A.: An. Farm. Bioquim. **3**:138, 1932; Rev. Soc. argent. de biol. **8**:631, 1932; Compt. rend. Soc. de biol. **92**:596, 1933.

122. Orias, O.: Biolog. Bull. **63**:427, 1933.

123. Orias, O.: Rev. Soc. argent. de biol. **10**:149, 1934; Quinto Cong. Nac. Med. Rosario **3**:263, 1934; Compt. rend. Soc. de biol. **117**:59, 1934.

124. Pasqualini, R. Q.: Rev. Soc. argent. de biol. 1935.

125. Ramirez Corria, C. M.: Rev. Soc. argent. de biol. **3**:227, 1927; Compt. rend Soc. de biol. **97**:591-593, 1927.

126. Re, P. M.: Rev. Soc. argent. de biol. **7**:503, 1931; Compt. rend. Soc. de biol. **109**:323, 1932.

127. Rietti, C. T.: Cong. Intern. Biol. Montevideo (Oct.) 1930; Arch. Soc. Biol. Montevideo, Supl. fasc. **2**:332, 1931.

128. Rietti, C. T.: J. Physiol. **77**:92 (Dec.) 1932.

129. Rietti, C. T.: Rev. Soc. argent. de biol. **10**:136, 1934; Quinto Cong. Nac. Med. Rosario **3**:243, 1934; Compt. rend. Soc. de biol. **117**:57, 1934.

130. Romaña, L.: Tesis Fac. Med. Veter. Bs. As. 1919.

131. Rubio, H. H.: Rev. Soc. argent. de biol. **3**:179, 1927; Compt. rend. Soc. de biol. **97**:589, 1927; Tesis Doct. Med. 1927.

132. Solari, L. A.: Segundo Cong. Nac. Med. Bs. As. **4**:841, 1922; Compt. rend. Soc. de biol. **88**:359, 1923.

133. Solari, L. A.: Quinto Cong. Nac. Med. Rosario **3**:303, 1934.

134. Abrams, M. I., and Gilligan, D. R.: Am. J. M. Sc. **188**:796, 1934.

135. Achard, Soulié, P.: Soc. Anat. 1931.

136. Alpern, D.: Ztschr. f. d. ges. exper. Med. **34**:324, 1923.

137. Anselmino, K. J., and Hoffmann, F.: Klin. Wchnschr. 2380, 1931.

138. Anselmino, K. J., and Hoffmann, F.: Klin. Wchnschr. **12**:1435, 1933.

139. Anselmino, K. J., and Hoffmann, F.: Klin. Wchnschr. 1148-1152, 1934; Arch. f. exper. Path. u. Pharmakol. 175-335, 1934; Ztschr. f. d. ges. exper. med. **94**:305, 1934.

140. Aschner, B.: Arch. f. d. ges. Physiol. **146**:1, 1912.

141. Assmann: Verein f. wissenschaftliche Heilkunde Königsberg i. Pr. 29 (Jan.) 1934.

142. Atkinson, F. A. B.: Acromegaly. John Bale, London, 1932.

143. Bailey, P. and Horrax, G.: Arch. Neurol. & Psychiat. **13**:423, 1925.

144. Bailey, P., and Bremer, F.: Arch. Int. Med. **28**:773, 1921.

145. Banting, F. G., and Gairns, S.: Am. J. Physiol. **77**:100 (June) 1926.

146. Barker, L. F.: Endokrinol. **17**:647 (Nov.) 1933.

147. Barnes, B. O.: Am. J. Physiol. **109**:5, 1934.

148. Barnes, B. O.; Dix, A. S., and Rogoff, J. M.: Proc. Soc. Exper. Biol. & Med. **31**:1145 (June) 1934.

149. Barnes, B. O., and Regan, J. F.: Proc. Am. Phys. Soc.; Am. J. Physiol. **105**:4, 1933; Endokrinol. **17**:522 (Sept.-Oct.) 1933.

150. Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Am. J. Physiol. **105**:559 (Sept.) 1933.

151. Barnes, B. O.; Regan, J. F., and Nelson, W. O.: J. A. M. A. **101**:926, 1933.

152. Barnes, B. O.; Scott, V. B.; Ferrill, H. W., and Rogoff, J. M.: Proc. Soc. Exper. Biol. & Med. **31**:524 (Feb.) 1934.

153. Baumann, E.: München med. Wchnschr. **43**:309, 1896.

154. Baumann, E., and Marine, D.: Proc. Soc. Exper. Biol. & Med. **29**:1220, 1932.

155. Bell, W. B.: The Pituitary. Bailliere edit. London, 1919.

156. Berblinger, W.: Hirsch. Handb. inn. Sekr. **1**, 1932.

157. Binet, L.; Verne, J., and Messimy, R.: Compt. rend. Soc. de biol. **116**:812, 1934.

158. Black, P. T.: J. Physiol. **84**:15, 1935.

159. Black, P. T.; Collip, J. B., and Thomson, D. L.: J. Physiol. **82**:385, 1934.

160. Blix, G., and Ohlin, C. A.: Skandin. Arch. f. Physiol. **51**:167, 1927.

161. Blum, L., and Schwab, H.: Compt. rend. Soc. de biol. **89**:195, 1923.

162. Boenheim, F., and Heimann, F.: Ztschr. f. d. ges. exper. Med. **83**:637-640, 1932.

163. Böhm, F.: Ztschr. f. d. ges. exper. Med. **84**:689, 1932.

164. Boller, R.: Uiberrak, K., and Falta, W: Wien. Arch. f. inn. Med. **25**:1, 1934.

165. Borchardt, L.: Ztschr. f. klin. Med. **66**:332, 1908.

166. Bourquin, H.: Proc. Am. Physiol. Soc. 1925; Am. J. Physiol. **76**:181, 1926; **80**:172, 1925.

167. Bronzini, A.: Arch. ital. de biol. **93**:112, 1935.

168. Brugsch, T.; Dresel, K., and Lewy, F. H.: Verhandl. d. Deutsch. Gesellsch. Inn. Med. 34 Kongr. 347, 1922; München. med. Wchnschr. **69**:796 (May 26) 1922.

169. Brull, L.: Rev. belge sc. méd. **2**:121 (Feb.) 1930.

170. Brull, L.: Presse méd. **41**:1267 (Aug.) 1933.

171. Brunn, P.: Ztschr. f. d. ges. exper. Med. **25**:170, 1921.

172. Burn, J. H., and Ling, H. W.: J. Physiol. **64**:22, 23, 1927; **69**:19, 1930.

173. Butts, J. S.; Cutler, C. H., and Deuel, H. J., Jr.: Proc. Soc. Exper. Biol. & Med. **31**:310, 1933; J. Biol. Chem. **105**:45 (April) 1934.

174. Calder, R. M.: Johns Hopkins Hosp. Bull. **50**:87 (Feb.) 1932; J. A. M. A. **98**:314 (Jan. 23) 1932.

175. Camus, J., and Gournay, J. J.: Compt. rend. Soc. de biol. **88**:694, 1923.

176. Camus, J., and Gournay, J. J.: Compt. rend. Soc. de biol. **90**:335 (Feb. 15) 1924.

177. Camus, J.; Gournay, J. J., and Le Grand, A.: Bull. Acad. Med. Paris, 1923-24; Presse méd. **33**:249 (Feb.) 1925.

178. Camus, J., and Roussy, G.: Compt. rend. Soc. de biol. **75**:485, 1913.

179. Camus, J., and Roussy, G.: Compt. rend. Soc. de biol. **76**:121, 299, 302, 344, 347, 773, 877, 1914; Presse méd. **22**:517, 1914.

180. Camus, J., and Roussy, G.: Rev. neurol. **38**:622 (June) 1922; Compt. rend. Soc. de biol. **83**:764, 901, 1578, 1920; Compt. rend. Soc. de biol. **85**:296, 1921; J. Physiol. Path. Génér. **20**:509, 1922; Rev. neurol. 29, 1922.

181. Camus, J., and Roussy, J.: Presse méd. **22**:517, 1914.

182. Camus, J.; Roussy, G., and Le Grand, A.: Compt. rend. Soc. de biol. **86**:1070 (May 20) 1922.

183. Caselli, A.: Riv. Sperim. Freniatria **26**:120, 1900; Studi Anat. e Sperim. sulla Fisiopatologia della ghiandola pituitaria, 1900, Calderini edit. Regzio, Emilia.

184. Chaikoff, I. L.; Reichert, F. L.; Larson, P. S., and Mathes, M. E.: Am. J. Physiol. **112**:493 (July) 1935.

185. Closs, K.; Loeb, L., and MacKay, E. M.: Proc. Soc. Exper. Biol. & Med. **29**:1170 (Nov.) 1931; J. Biol. Chem. **96**:585 (June) 1932.

186. Collip, J. B.: J. Mt. Sinai Hosp. **1**:28 (May-June) 1934.

187. Collip, J. B.: J. A. M. A. **104**:827, 916 (March 9) 1935.

188. Colwell, A. R.: Medicine, **6**:1 (Feb.) 1927.

189. Compère, A.: Arch. internat. de physiol. **36**:54 (Jan.) 1933; Compt. rend. Soc. de biol. **110**:92 (May 20) 1932.

190. Cope, O., and Marks, H. P.: J. Physiol. **83**:157 (Dec. 31) 1934.

191. Corkill, A. B.; Marks, H. P., and White, W. E.: J. Physiol. **80**:193 (Dec. 5) 1933.

192. Cowley, R. J.: J. Pharmacol. & Exper. Therap. **43**:287 (Oct.) 1931; Rev. de med. y cir. de la Habana, **37**:721 (Sept. 30) 1932.

193. Crowe, S. J.; Cushing, H., and Homans, J.: Bull. Johns Hopkins Hosp. **21**:127, 1910.

194. Curtis, G. M.: Arch. Int. Med. **34**:801 (Dec.) 1924.

195. Cushing, H.: Cameron Prize Lectures, Oxford Univ. Press, 1925.

196. Cushing, H., and Goetsch, E.: Am. J. Physiol. **27**:60, 1910.

197. Cushing, H.; Goetsch, E., and Jacobson, C.: Bull. Johns Hopkins Hosp. **22**:165, 1911.

198. Cushing, H.; Weed, L. H., and Jacobson, C.: Proc. Am. Phys. Soc. In Am. J. Physiol. **31**:XIII, 1912-13.

199. Daggs, R. G., and Eaton, A. G: Am. J. Physiol. **106**:299 (Nov.) 1933.

200. D'Amour, M. C., and Keller, A. D.: Proc. Soc. Exper. Biol. and Med. **30**:1175 (June) 1933.

201. Dandy, W. E., and Reichert, F. L.: Bull. Johns Hopkins Hosp. **37**:1 (July) 1925.

202. d'Antona, L., and Corbini, G.: Med. Klin. **27**:1177 (Aug. 7) 1931.

203. Davidoff, L. M., and Cushing, H.: Arch. Int. Med. **39**:751 (June) 1927.

204. Davis, L.: Ann. Surg. **100**:654 (Oct.) 1934; J. A. M. A. **104**:148 (Jan. 12) 1935.

205. Davis, L.; Cleveland, D., and Ingram, W. R.: Arch. Neurol. & Psychiat. **33**:592 (March) 1935.

206. Davis, B. L., Jr.; Hinsey, J. C., and Markee, J. E.: Endocrinology, **18**:382 (May-June) 1934.

207. Dawson, D. J., and Milne, A.: Quart. J. Exper. Physiol. **25**:69 (April) 1935.

208. Denis, W.: J. Biol. Chem. **9**:363, 1911.

209. Deuel, H. J., Jr.: Proc. Soc. Biol. Chem. In J. Biol. Chem. **105**:XIX (May) 1934.

210. Dewulf, A.: Compt. rend. Soc. de biol. **104**:798 (June 27) 1930.

211. Dewulf, A.: Arch. internat. de pharmacod. **40**:147, 1931.

212. di Guglielmo, G.: Boll. d. Soc. ital. di biol. sper. **2**:550, 1927.

213. Dingemanse, E., and Kober, S.: Endocrinol. **17**:149 (March-April) 1933.

214. Dobrin, M., and Lucinian, J. H., Jr.: J. Florida M. A. **21**:550 (June) 1935.

215. Dresel, K., and Lewy, F. H.: Ztschr. f. d. ges. exper. Med. **26**:187, 1922.

216. Eaton, A. G., and Daggs, R. G.: Proc. Am. Physiol. Soc. In Am. J. Physiol. **105**:29, 1933.

217. Eidelsberg, J.: Ann. Int. Med. **6**:201 (Aug.) 1932; Proc. Soc. Exper. Biol. & Med. **29**:959 (May) 1932.

218. Eitel, H., and Loeser, A.: Arch. f. exper. Path. u. Pharmakol. **167**:381, 1932; Klin. Wchnschr. **11**:1669 (Oct. 1) 1932; Internat. Clin. **2** (series 44): 66 (June) 1934.

219. Eitel, H.; Löhr, G., and Loeser, A.: Klin. Wchnschr. **12**:1776 (Nov. 11) 1933; Arch. f. exper. Path. u. Pharmakol. **173**:205, 1933.

220. Elek, L.: Ztschr. f. d. ges. exper. Med. **85**:227, 1932.

221. Evans, E. I.: Proc. Soc. Exper. Biol. & Med. **30**:1370 (June) 1933.

222. Evans, H. M: J. A. M. A. **101**:425 (Aug. 5) 1933.

223. Evans, H. M.; Meyer, K.; Simpson, M. E., and Reichert, F. L.: Proc. Soc. Exper. Biol. & Med. **29**:857 (April) 1932.

224. Evans, H. M.; Meyer, K.; Simpson, M. E.; Szarka, A. J.; Pencharz, R. I.; Cornish, R. E., and Reichert, F. L.: Memoirs University California, 1933, vol. 11.

225. Falta, W., and Nowaczynski, J.: Berl. klin. Wchnschr. **49**:1781, 1912.

226. Fasold, H.: Ztschr. f. d. ges. exper. Med. **92**:63, 1933.

227. Flater, A.: Med. Klin. **25**:426 (March 15) 1929.

228. Fluch, M.; Greiner, H., and Loewi, O.: Klin. Wchnschr. **13**:883 (June 16) 1934.

229. Fluch, M.; Greiner, H., and Loewi, O.: Arch. f. exper. Path. u. Pharmakol. **177**:167, 1935.

230. Foster, G. L.: J. Biol. Chem. **104**:497 (March) 1934.

231. Foster, G. L.; Gutman, A. B., and Gutman, E. B.: Proc. Soc. Exper. Biol. & Med. **30**:1028 (May) 1933.

232. Friedmann, F. F., and Maas, O.: Berl. klin. Wchnschr. **37**:1213 (Dec. 24) 1900.

233. Fry, H. A. B.: Quart. J. Med. **8**:278, 1915.

234. Fucci: Arch. di radiol., 1935.

235. Fujimoto, Y.: Folia pharmacol. Japon. **15**:10 (Nov. 20) 1932.

236. Funk, C.: Proc. Soc. Biol. Chem. In J. Biol. Chem. **100**: XIV (May) 1933.

237. Funk, C.: J. Biol. Chem. **105**:XXIX (May) 1934.

238. Funk, C., and Zedlrow, P.: XIV Cong. Intern. Fisiol. Roma, 1932, p. 142; Arch. di sc. biol. **18**:142, 1933.

239. Funk, C.; Zedlrow, P., and Funk, I. C.: Arch. internat. de pharmacod. **49**:189 (Nov. 30) 1934.

240. Gaebler, O. H.: J. Biol. Chem. **81**:41 (Jan.) 1929.

241. Gelling, E. M. K.; Britton, S. W., and Calvery, H. O.: J. Pharmacol. & Exper. Therap. **36**:235 (June) 1929.

242. Gelling, E. M. K.; Campbell, D., and Ishikawa, Y.: J. Pharmacol. & Exper. Therap. **31**:247 (July) 1927.

243. Gemelli, A.: Arch. ital. de biol. **50**:157, 1908-09.

244. George, E.: Ztschr. f. d. ges. exper. Med. **72**:303, 1930.

245. Goetsch, E.; Cushing, H., and Jacobson, C.: Bull. Johns Hopkins Hosp. **22**:165, 1911.

246. Goldzieher, M. A.; Sherman, I., and Alperstein, B. B.: Endokrinol. **18**:505, 1934.

247. Gondard, L.; Hedon, L., and Loubatières, A.: Compt. rend. Soc. de biol. **119**:711, 1935.

248. Gournay, J. J.: These Fac. Med., Paris, 1925.

249. Grab, W.: Arch. f. exper. Path. u. Pharmakol. **167**:413, 1932.

250. Grab, W.: Klin. Wchnschr. **12**:1102 (July 15) 1933; Arch. f. exper. Path. u. Pharmakol. **172**:588, 1933.
251. Graubner, W.: Ztschr. f. klin. Med. **101**:249, 1924-25.
252. Greeley, P. O.: Proc. Soc. Exper. Biol. & Med. **32**:1070 (April) 1935.
253. Halliburton, W. D.; Candler, J. P., and Sikes, A. W.: Quart. J. Exper. Physiol. **2**:229, 1909.
254. Hanchett, McM.: Am. J. M. Sc. **163**:685, 1922.
255. Handelsmann, L., and Horsley, V.: Brit. M. J. **2**:1150, 1911.
256. Hantschmann: Verein. f. wissensch. Heilk. Königsberg i. Pr., 1933.
257. Hantschmann: Deutsches Arch. f. klin. Med. **176**:397, 1934.
258. Harrow, B.; Chamelin, I. M., and Mazur, A.: Am. J. Physiol. **109**:436 (Sept.) 1934.
259. Harrow, B.; Naiman, B.; Chamelin, I. M., and Mazur, A.: Proc. Soc. Exper. Biol. & Med. **31**:940 (May) 1934.
260. Hartman, C. G.; Firor, W. M., and Geiling, E. M. K.: Am. J. Physiol. **95**:662 (Dec.) 1930.
261. Hédon: Bruxelles-Méd. **17**:38, 1935.
262. Heller, J.: Arch. f. exper. Path. u. Pharmakol. **157**:298, 1930.
263. Herman, K.: München. med. Wchnschr. **81**:1460 (Sept. 21) 1934.
264. Hertz, W.: Klin. Wchnschr. **12**:1144 (July 22) 1933.
265. Hetzel, K. S.: Lancet **1**:440 (Feb. 27) 1926.
266. Hidekazu, K.: Japan. J. M. Sc., 4. Pharmacol. **8**:74, 1934.
267. Hildebrand, K. H.: Klin. Wchnschr. **14**:951 (July 6) 1935.
268. Hill, R. T.; Corkill, A. B., and Parkes, A. S.: Proc. Roy. Soc. Lond. **116** (series B): 208 (Nov. 1) 1934.
269. Himwich, H. E.; Haynes, F. W., and Spiers, M. A.: Proc. Soc. Exper. Biol. & Med. **28**:332 (Dec.) 1930.
270. Himwich, H. E., and Keller, A. D.: Am. J. Physiol. **93**:658, 1930.
271. Hirayama, C.: Mitt. jap. Gynäk. **29**; Deutsche Zusammenfassung, **32**, 1934.
272. Hoffmann, F., and Anselmino, K. J.: Klin. Wchnschr. **10**:2383 (Dec. 26) 1931.
273. Hoffmann, F., and Anselmino, K. J.: Klin. Wchnschr. **12**:1436 (Sept. 16) 1933.
274. Holden, R. F., Jr.: Proc. Soc. Exper. Biol. & Med. **31**:773 (April) 1934.
275. Hoskins, E. R., and Hoskins, M. M.: Endocrinol. **4**:1 (Jan.-March) 1920.
276. Houssay, B. A., and Lewis, J. T.: Rev. Asoc. méd. argent. **34**:1099 (Nov.) 1921 (Soc. de biol. **2**:261); Compt. rend. Soc. de biol. **85**:1209, 1921.
277. Houssay, B. A., and Molinelli, E. A.: Rev. Soc. argent. de biol. **1**:600, 1925; abs. in Compt. rend. Soc. de biol. **93**:1454 (Dec. 11) 1925.
278. Hrubetz, M. C.: Proc. Soc. Exper. Biol. & Med. **32**:842 (March) 1935.
279. Ichijo, T.: Jap. J. M. Sc. Tr., IV, Pharmacol. **8**:85 (Aug.) 1934.
280. Ingram, W. R., and Barris, R. W.: Endocrinol. **19**:432 (July-Aug.) 1935.
281. Jacobson, C.: Am. J. Physiol. **52**:233, 1920.
282. de Jaegher, M., and van Bogaert, A.: Compt. rend. Soc. de biol. **118**:1035, 1935.
283. Johns, W. S.; O'Mulvenny, T. O.; Potts, E. B., and Laughton, N. B.: Tr. Roy. Soc. Canada. **20**:243, 1926.
284. Johns, W. S.; O'Mulvenny, T. O.; Potts, E. B., and Laughton, N. B.: Am. J. Physiol. **80**:100 (March) 1927.
285. Jonas, V.: Ztschr. f. d. ges. exper. Med. **94**:195, 1934.
286. Karlik, L. N.: Personal communication.
287. Karlik, L. N., and Robinson, J. A.: Arch. argent. de neurol. **12**:61 (March-April) 1935.
288. Keeton, R. W., and Becht, F. C.: Am. J. Physiol. **39**:109, 1915; **49**:248, 1919.
289. Képinov, L.: Compt. rend. Soc. de biol. **116**:145, 1934.
290. Képinov, L.: Compt. rend. Soc. de biol. **116**:833, 1934.
291. Képinov, L., and Guillaumie, M.: Compt. rend. Soc. de biol. **115**:1564, 1934; **119**:149, 1935.
292. Klug, W.: Deutsche Ztschr. f. Chir. **212**:5, 1928.
293. Kobayashi, K.: Jap. J. M. Sc. Tr., IV, Pharmacol. **5**:56, 1931.
294. Koster, S., and Geesink, A.: Arch. néerl. de physiol. **13**: 601, 1928; Arch. f. d. ges. Physiol. **222**:293, 1929.
295. Kraus, E. J.: Virchows Arch. f. path. Anat. **228**:68, 1920; Beitr. z. path. Anat. u. z. allg. Path. **68**:258, 1921.
296. Krauss, E.: Klin. Wchnschr. **5**:700 (April 16) 1926.
297. Kusunoki, G.: Folia endocrin. japon. 3 (No. 5): 24 (Dec. 22) 1927.
298. Kusunoki, G., and Nakamura, K.: Klin. Wchnschr. **13**:1832 (Dec. 22) 1934.
299. Kutz, R. L.; Selye, H.; Denstedt, O.; Bachman, C.; Thomson, D. L., and Collip, J. B.: Proc. Am. Physiol. Soc. In Am. J. Physiol. **109**:66, 1934.
300. Kylin, E.: Med. Klin. **29**:1004 (July 21) 1933; **30**:153 (Feb. 2) 1934.
301. Kylin, E.: Ztschr. f. Kreislaufforsch. **27**:1 (Jan. 1) 1935; Klin. Wchnschr. **14**:470, 1935.
302. Labbé, M.; Escalier, A., and Dreyfus, G.: Ann. de méd. **29**:222 (March) 1931.
303. Labbé, M.; Escalier, A., and Uhry, P.: Compt. rend. Soc. de biol. **114**:890, 1933.
304. Labbé, M., and Petresco, M.: Soc. Anat., 1932; Ann. d'anat. path. **11**:761 (Nov.) 1934.
305. Le Grand, A.: Paris, 1935, edit. Amédee Le Grand.
306. Lhermitte, J.: Ann. de méd. **11**:89 (Feb.) 1922; Rev. neurol. **1**:920 (June) 1934.
307. Lhermitte, J.: Rev. neurol. **1**:920 (June) 1934.
308. Lhermitte, J., and Pagniez, P.: Presse méd. **42**:649, 1934.
309. Lhermitte, J., and Roeder: Rev. neurol. **38**:758, 1922.
310. Leiner, G.: Ztschr. f. d. ges. exper. Med. **94**:84, 1934.
311. Leloir, L. F: Rev. Soc. argent. de biol. **10**:216 (Aug.) 1934; Compt. rend. Soc. de biol. **117**:459, 1934.
312. Lépine, J. R.: Le Diabète Sucré. Paris, Felix Alcan, éditeur, 1909.
313. Leschke, E.: Ztschr. f. klin. Med. **87**:201, 1918.
314. Leschke, E.: Deutsche med. Wchnschr. **46**:959, 996, 1920.
315. Leschke, E.: Erkrankungen des vegetativen Nervensystem. Leipzig, Kabitsch, 1931; Ann. de med. **33**:261 (March) 1933.
316. Lewis, J. T., and Turcatti, E.: Rev. Soc. argent. de biol. **9**:115 (May) 1933; Compt. rend. Soc. de biol. **114**:103, 1933.
317. Loeb, L.: Schilddrüse, Jod und Hypophysenvorderlappen. Klin. Wchnschr. **11**:2121, 2125, 2156, 2160, 1932.
318. Loeser, A.: Arch. f. exper. Path. u. Pharmakol. **163**:530, 1931.
319. Loeser, A.: Med. Gesellsch. Frieburg i. Br. (Offizielles Protokoll), 1933; Klin. Wchnschr. **13**:83 (Jan. 20) 1934.
320. Long, M. L.; Hill, E., and Bischoff, F.: Am. J. Physiol. **102**:402 (Nov.) 1932.
321. Long, M. L.; Hill, E., and Bischoff, F.: See ref. 320.
322. Long, C. N. H., and Lukens, F. D. W.: Science. **79**:569 (June 22) 1934; Proc. Soc. Exper. Biol. & Med. **32**:326 (Nov.) 1934.
323. Long, C. N. H., and Lukens, F. D. W.: Proc. Soc. Biol. Chem. In J. Biol. Chem. **109**:LVI (May) 1935; Proc. Soc. Exper. Biol. & Med. **32**:743 (Feb.) 1935.
324. Lucke, H.: Ztschr. f. Konstit. lehre. **14**:130, 1929.
325. Lucke, H.: Ztschr. f. klin Med. **122**:23, 1932; Klin. Wchnschr. **11**:1678, 1988, 1932.
326. Lucke, H.: Arch. f. exper. Path. u. Pharmakol. **170**:166, 1933; Ztschr. f. klin. Med. **125**:361, 1933; Med. Gesellsch. Göttingen, 1933; Verh. 45 Kongr. inn. Med., 1933, p. 164.
327. Lucke, H.: Ergebn. d. inn. Med. u. Kinderh. **46**:94, 1934.
328. Lucke, H., and Hahndel, H: Ztschr. f. d. ges. exper. Med. **91**:689, 696, 704, 1933.
329. Lucke, H.; Heydemann, E. R., and Berger, O.: Ztschr. f. d. ges. exper. Med. **90**:120, 1933; **92**:711, 1934.
330. Lucke, H.; Heydemann, E. R., and Duensing, F.: Ztschr. f. d. ges. exper. Med. **91**:106, 1933.
331. Lucke, H.; Heydemann, E. R., and Hahndel, H.: Ztschr. f. d. ges. Med. **91**:483, 492, 1933.
332. Lucke, H.; Heydemann, E. R., and Hechler, R.: Ztschr. f. d. ges. exper. Med. **87**:103, 1933.
333. Lucke, H.; Heydemann, E. R., and Hechler, R.: Ztschr. f. d. ges. exper. Med. **88**:85, 1933.
334. Lucke, H., and Hroeger: Ztschr. f. d. ges. exper. Med. Cit. por Lucke.
335. Lyall, A., and Innes, J. A.: Lancet **1**:318, 1935.
336. McArthur, C. G.: J. Am. Chemie. Soc. **41**:1225-40, 1919.
337. McPhail, M. K.: Proc. Roy. Soc. Lond. **45**:117, 1935. Ser. B
338. Magistris, H.: Endokrinol. **11**:176, 1932; Compt. rend. Soc. de biol. **111**:397, 1932.
339. Magistris, H.: Wien. klin. Wchnschr. **46**:908 (July) 1933.
340. Magistris, H.: Arch. f. exper. Path. u. Pharmakol. **178**:15, 1935.
341. Magoun, H. W.; Barris, R. W., and Ranson, S. W.: Anat. Record **52**:24, 1932.
342. Mahoney, W.: Am. J. Physiol. **109**:475, 1934.
343. Marañon, G.: An. de med. int. **1**:45 (Jan.) 1932.
344. Marinesco, G., and Nicolesco, J.: Compt. rend. Soc. de biol. **116**:557, 1934.
345. Marinesco, G., and Paulian, E. D.: Bull. Acad. de méd. Par. **93**:166 (Feb. 19) 1925.
346. Marx, H.: Klin. Wchnschr. **6**:2036 (Oct.) 1927.
347. May, E.; Lhermitte, J., and Kaplan, M.: Presse méd. **46**:862 (June 16) 1931.
348. Mazer, C.; Meranze, D. R., and Israel, S. L.: J. A. M. A. **105**:257 (July 27) 1935.
349. Meythaler, F., and Schroff, G.: Klin. Wchnschr. **14**:893, 1935.
350. Miki, S., and Fukuoka-Ikwadaigaku-Zasshi: **25**:35, 1932.
351. Nakamura, K., and Fukuoka-Ikwadaigaku-Zasshi: **24**:18, 1931; Zusammenfassung, 18-19.
352. Nelson, W. O.: Endocrinol. **19**:187, 1935.
353. Nelson, W. O., and Overholser, M. D.: Proc. Soc. Exper. Biol. & Med. **32**:150, 1934.
354. Nelson, W. O.; Turner, C. W., and Overholser, M. D.: Am. J. Physiol. **112**:714, 1935.
355. Nicolesco, I., and Ralleanu, D.: Compt. rend. Soc. de biol. **95**:122 (June 18) 1926.
356. Nitzescu, I. I., and Benetato, G.: Compt. rend. Soc. de biol. **105**:67 (June 26) 1930; **107**:377, 1931.
357. Noether, P.: Klin. Wchnschr. **11**:462, 1932.
358. Oppenheimer, A.: Klin. Wchnschr. **9**:17 (Jan.) 1930.
359. Orias, O.: Biol. Bull. **63**:477, 1932.
360. Orru, M.: Boll. Soc. Ital. Biol. Sperim. **9**:1055, 1934; Fol. Gynac. **31**:311, 1934.
361. Perémy, G.: Klin. Wchnschr. **14**:92 (Jan. 19) 1935.
362. Phillips, R. A., and Robb, P.: Proc. Am. Phys. Soc. 1934; Am. J. Physiol. **109**:82, 1934.
363. Raab, W.: Ztschr. f. d. ges. exper. Med. **49**:179, 1926; **62**:366, 1928; Klin. Wchnschr. **13**:81, 1928; Wien. Arch. Med. **17**:439, 1929; Endokrinol. **14**:150, 1930; Ztschr. f. d. ges. exper. Med. **89**:588, 1933; Wien. klin. Wchnschr. **47**:1284, 1934; Klin. Wchnschr. **13**:81 (Feb.) 1934; Vechnik Endokrinol, Moscu, **4**:224, 1934; Ztschr. f. d. ges. exper. Med. **94**:284, 1934.

364. Raab, W., and Kerschbaum, E.: Ztschr. f. d. ges. exper. Med. **90**:729, 1933.
365. Rabens, I., and Lifschitz, J.: Am. J. Physiol. **36**:47, 1915.
366. Rau, L.: Lancet **1**:1502 (June 29) 1935.
367. Regan, J. F., and Barnes, B. O.: Am. J. Physiol. **105**:83, 1933; Science **77**:214 (Feb. 24) 1933.
368. Repetto, R. L.: Trab. adscrip. Fac. Medic. Bs. As., 1931.
369. Richter, C. P.: Am. J. Physiol. **110**:439 (Dec.) 1934.
370. Riddle, O., and Dotti, L. B.: Proc. Soc. Exper. Biol. & Med. **32**:507 (Dec.) 1934.
371. Rogers, F. T.: Am. J. Physiol. **76**:284, 1923; **68**:499 (May) 1924.
372. Rogers, F. T.: Am. J. Physiol. **86**:639 (Oct.) 1928.
373. Romano, S.: Rassegna internaz. di clinica a terap. 936, 1933; Rev. Sud-Amer. Endocrin. Immunol. Quimioter, **18**:108, 1935.
374. Roussy, G.: Ann. Medec. **18**:407, 1925.
375. Roussy, G., and Gournay, J. J.: Traité Physiol. norm Pathol. **4**:403, 1928.
376. Ruff, G.: Folia Biol. 131, 1933.
377. Ruff, G.: Rev. d. Inst. bact. **6**:220 (March) 1934.
378. Sachs, E., and MacDonald, M. E.: Arch. Neurol. & Psychiat. **13**:335 (March) 1925.
379. Saito, G.: Nikon Naika Gakkai Zasshi **14**, 1926.
380. Saito, G.: Fol. endocrin. japon **1**:55, 1934.
381. Sakamoto, A., and Saito, G.: Ztschr. f. d. ges. exper. Med. **80**:601, 1932.
382. Salus, F.: Ztschr. f. d. ges. Neurol. u. Psychiat. **148**:574, 1933.
383. Samaan, A.: Proc. Phy. Soc. 1935; J. Physiol. **84**, 1935.
384. Schäfer, E. A., and Herring, P. T.: Proc. Roy. Soc. Lond. 199, 1906, Ser. B.
385. Schäfer, E. A., and Magnus: Proc. Physiol. Soc. 9-10, 1910; in J. Physiol. 27-9, 1901-02.
386. Schittenhelm, A.: Klin. Wchnschr. **14**:401 (March 23) 1935.
387. Schittenhelm, A., and Eisler, B.: Klin. Wchnschr. **9**:1092, 1783, 1932; Ztschr. Exper. Med. **86**:275-89, 294, 1933.
388. Schittenhelm, A., and Harpuder, K.: Ztschr. f. d. ges. exper. Med. **27**:50, 1922.
389. Schneider, E., and Widmann, E.: Deutsche Ztschr. f. Chir. **241**:778, 1933.
390. Schnitzler, J., and Ewald, K.: Wien. klin. Wchnschr. **9**:657, 1896.
391. Schockaert, J. A., and Foster, G. L.: J. Biol. Chem. **95**:89 (Feb.) 1932; Am. J. Anat. **49**:279 (Jan.) 1932.
392. Schretter, G., and Nevinny, H.: Arch. Gynäk. **143**:465, 1930.
393. Schultze, K. W.: Arch. f. Gynäk. **155**:327, 1934.
394. Schultz Ortiz, G., and Rothmann, B.: Semana méd. **39**:1630, 1932.
395. Schwab, E.: Zentr. allg. Pathol. u. Pathol. Anat. **33**:482, 1923.
396. Scott, V. B.; Ferrill, H. W.; Rogoff, J. M., and Barnes, B. O.: Proc. Am. Phys. Soc. 1934; Am. J. Physiol. **109**:95, 1934.
397. Seamen, E. C.: J. Biol. Chem. **43**:1 (Aug.) 1920.
398. Selle, W. A.; Westra, J. J., and Johnson, J. B.: Proc. Soc. Exper. Biol. & Med. **31**:949, 1934; Endokrinol. **19**:97 (Jan.-Feb.) 1935.
399. Shapiro, P. F.: Arch. Path. **11**:22 (Jan.) 1931.
400. Shpiner, L. B., and Soskin, S.: Am. J. Physiol. **109**:97, 1934.
401. Silajeiva, E.: Ztschr. med. Ciklu- **3**:259-266; u. franz. Zusammenfassung 266-267, 1933.
402. Silberstein, F., and Gottdenker, F.: Klin. Wchnschr. **13**:1434 (Oct. 6) 1934.
403. Silberstein, F.; Gottdenker, F., and Hohenberg, E.: Klin. Wchnschr. **13**:595 (April 21) 1934.
404. Silver, S.: Arch. Int. Med. **51**:175, 1933.
405. Simpson, and Hunter: Quart. J. Exper. Physiol. **3**:121, 1910.
406. Smith, P. E.: Am. Anat. Mem. **11**, 1926.
407. Smith, P. E., and Cheney, G.: Endokrinol. **5**:448, 1921.
408. Snoeck, J. J.: Arch. internat. de med. exper. **7**:349, 1932.
409. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Am. J. Physiol. **109**:155, 1934.
410. Steggerda, F. R.: Am. J. Physiol. **98**:255, 1931.
411. Steggerda, F. R., and Essex, H. E.: Am. J. Physiol. **109**:102, 1934; Proc. Soc. Exper. Biol. & Med. **32**:425 (Dec.) 1934.
412. Steggerda, F. R., and Freedman, H. E.: Proc. Soc. Exper. Biol. & Med. **30**:623, 1933.
413. Steppouun, O.: Wien. Arch. Med. **26**:87, 1934.
414. Steppouun, O.; Petrova, A.; Kalachnikowa, I., and Troufanoff, A.: Technik. Endocrin. **4**:223, 1934.
415. Stewart, G. N., and Rogoff, J. M.: Am. J. Physiol. **65**:319, 1923.
416. Sturm, A.: Zentralbl. f. inn. Med. **55**:897, 1934; Ztschr. f. d. ges. exper. Med. **93**:490, 1934.
417. Sturm, A., and Buchholz, B.: Deutsches Arch. f. klin. Med. **161**:227, 1928.
418. Sturm, A., and Schneeberg, R.: Ztschr. f. d. ges. exper. Med. **86**:665, 1933.
419. Teel, H. M., and Watkins, O.: Am. J. Physiol. **89**:662, 1929.
420. Thannhauser, S. J., and Curtius, F.: Deutsches Arch. f. klin. Med. **143**:287, 1923.
421. Towne, E. B.: Proc. Soc. Exper. Biol. & Med. **19**:306, 1922.
422. Troufanoff, A.: Endokrinol. (Moscu) **4**:223, 1934.
423. Turcatti, E. S.: Rev. Soc. argent. de biol. **5**:173, 1929; Compt rend. Soc. de biol. **102**:466, 1929.
424. Ulrich, H.: Arch. Int. Med. **43**:745, 1929.
425. Urechia, C. I., and Elekes, N.: Encephale, 1924.
426. Vassale, G., and Sacchi, E.: Riv. sper. di freniat. **18**:525, 1892; **20**:83, 1894; Arch. Ital. Biol. **18**:385, 1893.
427. Velhagen, K.: Klin. Wchnschr. **8**:1577, 1929.
428. Verney, E. B.: Proc. Roy. Soc. **99**:487, 1926.
429. Vernon, O.: Centralbl. Pathol. u. Pathol. Anat. **31**:521, 1921.
430. Wells, H. G.: J. Biol. Chem. **7**:259, 1910.
431. White, W. E.: Proc. Roy. Soc. **114**:64, 1933.
432. Wilder, J.: Wien. Klin. Wchnschr. 1518, 1929; Deutsche Ztschr. f. Nervenh. **112**:192, 1930; Ztschr. f. d. ges. exper. Med. **76**:136, 1931.
433. Wittgenstein, A.: Arch. f. d. ges. Physiol. **229**:299, 1932.
434. Yater, W. M.: Arch. Int. Med. **41**:883, 1928.
435. Yriart, M.: Rev. Soc. argent. de biol. **6**:297, 1930; Compt. rend. Soc. de biol. **105**:128, 1930.
436. Zunz, E., and La Barre, J.: Compt. rend. Soc. de biol. **119**:1174, 1935.
437. Zwarenstein, H., and Rosman, L. P.: Quart. J. Exper. Physiol. **22**:45, 1932.

HEALTH FOODS

Health foods on sale at Washington, D. C., and Boston, labeled to give the impression they were foods possessing special remedial properties, have been seized by the Food and Drug Department on charges of misbranding.

"Correcol," a mixture of seeds similar to psyllium, with a vegetable gum, labeled as a "colon food," and that it would set up normal intestinal activity, was seized on the allegation that the ingredients had no food value and that the latter claim was not justified.

On the grounds that the ingredients provided no more potassium than in the normal wholesome diet, and that representation of the article as a "health product" was unwarranted, "Hauser Potassium Broth," made of dried seaweed, alfalfa, okra, potato starch, beet and rhubarb leaves, was seized.

"Slim," described as "a delicious non-habit forming beverage," was seized on the grounds that it is not a beverage and that claims for the reduction of weight by its use were unwarranted.

Described as possessing special health-giving properties, "Vege-Broth" was seized on the grounds that it contained minerals in no greater concentration of effectiveness than in the average diet.

"Vegetrate Formula BF-1" and "Syl-Way" were seized for misbranding. Claims of mineral content of the former were alleged to be false and curative claims in case of hyperacidity, bloat and gas, were held to have been made with intent to defraud. The Department challenges the claims made for "Syl-Way" as "nature's regulator" in respect to the treatment of intestinal inflammation and other ailments.—*Bulletin, Boston Better Business Bureau.*

THE NEW HAMPSHIRE MEDICAL SOCIETY

THE ONE HUNDRED AND FORTY-FIFTH ANNUAL MEETING

Hotel Carpenter, Manchester, N. H., Tuesday and Wednesday, May 26-27, 1936

OFFICERS FOR 1935-1936

President

Clifton S. Abbott, Laconia.

Vice-President

Frank E. Kittredge, Nashua.

Secretary-Treasurer

Carleton R. Metcalf, Concord.

Councilors

	Term Expires
John A. Hunter, Strafford County	1936
*Abram W. Mitchell, Rockingham Co.	1936
Richard E. Wilder, Coos County	1937
Charles E. Smith, Carroll County	1937
Clifton S. Abbott, Belknap County	1938
Arthur T. Downing, Grafton County	1938
Frank M. Dinsmoor, Cheshire County	1939
Emery M. Fitch, Sullivan County	1939
Henry H. Amsden, Merrimack County	1940
Timothy F. Rock, Hillsborough County	1940

*Deceased.

Trustees

Henry O. Smith, Hudson	1936
Thomas W. Luce, Portsmouth	1937
Alpha H. Harriman	1938

Delegate to A. M. A.

Deering G. Smith, Nashua.

Alternate Delegate to A. M. A.

Emery M. Fitch, Claremont.

Necrologist

Clarence E. Dunbar, Manchester.

STANDING COMMITTEES

Advisory Committee on Jurisprudence

Clifton S. Abbott, Belknap County; Fred E. Clow, Carroll County; Osmon H. Hubbard, Cheshire County; Joseph J. Cobb, Coos County; Arthur T. Downing, Grafton County; David W. Parker, Hillsborough County; Robert J. Graves, Merrimack County; Thomas W. Luce, Rockingham County; Louis W. Flanders, Strafford County; Henry C. Sanders, Jr., Sullivan County; Carleton R. Metcalf, Concord, Chairman.

Amendments to Constitution and By-Laws

Henry O. Smith, Fred E. Clow, Thomas W. Luce.

Control of Cancer

George C. Wilkins, Howard N. Kingsford, George F. Dwinell.

Medical Economics

Timothy F. Rock, 1936; John F. Gile, 1937; Frederic P. Lord, 1938.

Medical Education and Hospitals

John P. Bowler, James W. Jameson, Harris E. Powers.

Mental and Social Hygiene

Charles H. Dolloff, Benjamin W. Baker, Charles A. Weaver.

New England Medical Council

Clifton S. Abbott, President; Carleton R. Metcalf, Secretary-Treasurer; David W. Parker (1936); Harry O. Chesley (1937); Robert H. Brooks (1938).

Public Relations

Samuel T. Ladd, Charles Duncan, the President, the Vice-President, the Secretary-Treasurer.

Publication

Carleton R. Metcalf, Henry H. Amsden, Warren H. Butterfield.

Scientific Work

Carleton R. Metcalf, Frederick P. Scribner, Richard W. Robinson.

Tuberculosis

Robert B. Kerr, Robert M. Deming, Arthur L. Wallace.

SPECIAL COMMITTEES

Advisory Committee on Medical Relief

Robert J. Graves, John P. Bowler, Clarence O. Coburn.

Child Health

Colin C. Stewart, Jr., Travis P. Burroughs, Lloyd H. Cogswell.

Maternity and Infancy

Robert O. Blood, Benjamin P. Burpee, Chester F. McGill.

Medical Liability

Henry C. Sanders, Jr., David W. Parker, Arthur T. Downing.

MONDAY, MAY 25, 7:30 P.M.

Hotel Carpenter

HOUSE OF DELEGATES

Speaker, James B. Woodman, Franklin Falls.
Vice-Speaker, Cleon W. Colby, Exeter.

Delegates to N. E. States' Meetings

Maine: Charles F. Nutter, Nashua; Joseph J. Cobb, Berlin.
Vermont: Oscar C. Young, Charlestown; Elmer M. Miller, Woodsville.
Massachusetts: Harry W. Savage, Lebanon; John F. Holmes, Manchester.
Rhode Island: Benjamin E. Sanborn, Manchester; George M. Crowell, Suncook.
Connecticut: A. Philip LaFrance, Laconia; Osmon H. Hubbard, Keene.

HOUSE OF DELEGATES

The President, ex-officio.
The Vice-President, ex-officio.
The Secretary-Treasurer, ex-officio.

Belknap County

Richard W. Robinson, Laconia.
Raymond J. Turley, Meredith.

Carroll County

William J. Paul Dye, Wolfeboro.
Francis J. C. Dube, Center Ossipee.

Cheshire County

Osmon H. Hubbard, Keene.
Frank M. Dinsmoor, Keene.

Coos County

Richard E. Wilder, Whitefield.
James A. Ferguson, Lancaster.

Grafton County

Leslie E. McKinlay, No. Haverhill.
Leslie K. Sycamore, Hanover.
Robert M. Deming, Glencliff.

Hillsborough County

Joseph E. Larochelle, Manchester.
Roland J. Joyce, Nashua.
Deering G. Smith, Nashua.
Clarence E. Dunbar, Manchester.
Charles H. Cutler, Peterborough.

Merrimack County

Henry H. Amsden, Concord.
Warren H. Butterfield, Concord.
James B. Woodman, Franklin Falls.

Rockingham County

Lawrence R. Hazzard, Portsmouth.
Oscar B. Gilbert, Exeter.

Strafford County

Harry O. Chesley, Dover.
Jeremiah J. Morin, Rochester.

Sullivan County

Henry C. Sanders, Jr., Claremont.
Donald C. Moriarty, Newport.

TUESDAY, MAY 26, 10:00 A.M.

Standard Time

GENERAL MEETING

1. *Call to order by the President.* Clifton S. Abbott, Laconia.

2. *The Irritable Colon: Diagnosis and Treatment by the General Practitioner.* J. Dunbar Shields, Concord.

Discussion opened by Clarence O. Coburn, Manchester; Fred E. Clow, Wolfeboro.

3. *Artificial Pneumothorax in the Treatment of Tuberculosis.* John D. Spring, Nashua.

Discussion opened by Robert B. Kerr, Manchester; Robert M. Deming, Glencliff.

4. *Diuretics and What They Do.* Henry A. Christian, Boston. Hersey Professor of Theory and Practice of Physic, Harvard Medical School.

Discussion opened by Bruce Snow, Manchester; Walter F. Taylor, Keene.

TUESDAY, MAY 26, 2:00 P.M.

Standard Time

1. *Presentation of 50-year Membership Gold Medal to* Ellen A. Wallace, Manchester.

2. *Introduction of Doctors who have been in practice 50 years.* Frederick L. Hawkins, Meredith; J. Franklin Robinson, Manchester.

3. *The President's Address.* Clifton S. Abbott, Laconia.

4. *Symposium on Pediatrics.*

a. Medical Aspects. Richard M. Smith, Boston. Assistant Professor of Pediatrics, Harvard Medical School.

Discussion opened by Ursula G. Sanders, Concord.

b. Surgical Aspects. William E. Ladd, Boston. Clinical Professor of Surgery, Harvard Medical School.

Discussion opened by MacLean J. Gill, Concord.

c. The Prevention and Modification of Certain Communicable Diseases. R. Cannon Eley, Boston.

Discussion opened by Abbott L. Winograd, Nashua.

WEDNESDAY, MAY 27, 10:00 A.M.
Standard Time

1. *Reception of Visiting Delegates.*

2. *Problems in the Diagnosis and Treatment of Bronchiectasis.* M. Dawson Tyson, Hanover.

Discussion opened by Robert M. Deming, Glencliff; Leslie K. Sycamore, Hanover.

3. *More Rational Methods in the Prevention and Control of Eclampsia.* J. O. Arnold, Philadelphia. Professor of Obstetrics, Temple University.

Discussion opened by Benjamin P. Burpee, Manchester; Robert O. Blood, Concord.

4. *Public Relations of the Medical Profession.* Morris Fishbein, Chicago. Editor, *Journal of the American Medical Association.*

WEDNESDAY, MAY 27, 2:00 P.M.
Standard Time

1. *Introduction of New President.*

2. *Report of House of Delegates.*

3. *Report of Trustees.*

4. *Recent Advances in Urologic Surgery, Including Renal and Prostatic Surgery. Experiences with a New Operation for Impotence.* Oswald S. Lowsley, New York City.

Discussion opened by Elmer J. Brown, Manchester; Richard W. Robinson, Laconia.

5. *Coronary Disease, Including Angina Pectoris.* William D. Stroud, Philadelphia. Professor of Cardiology, Jefferson Medical College.

Discussion opened by Granville E. Hoffses, Manchester; Harry T. French, Hanover.

WEDNESDAY, MAY 27, 6:30 P.M.
Standard Time

THE BANQUET

Anniversary Chairman

Richard W. Robinson, Laconia.

Guest Speakers

His Excellency, H. Styles Bridges, Governor of New Hampshire.

Dr. Clifton S. Abbott, President, N. H. Medical Society.

Dr. Morris Fishbein, "Medicine in the Changing Social Order."

COMMITTEE ON ARRANGEMENTS

General Chairman—Adolphe J. Provost.
Vice-Chairman—Benjamin E. Sanborn.
Secretary—Harris E. Powers.
Treasurer—Elmer J. Brown.

Location—Alexandre Barbeau.
Program—Daniel J. Sullivan.
Reception—George V. Fiske.
Banquet—Walter A. Bartlett
Exhibition—George F. Dwinell.
Finance—Elmer J. Brown.
Publicity—Murray H. Towle.
Hospital—Damase Caron.

List of Commercial Exhibitors at the time of going to press:

Bard-Parker Company, Inc., Danbury, Conn.
Elmer N. Blackwell, Portland, Maine.
Boss & Seiffert Company, Inc., Providence, R. I.
Canada Dry Ginger Ale, Inc., Chelmsford, Mass.
Otis Clapp & Son, Inc., Boston, Mass.
Davies, Rose & Co., Ltd., Boston, Mass.
The Denver Chemical Mfg. Co., New York, N. Y.
Endo Products, Inc., New York, N. Y.
George C. Frye Company, Portland, Maine.
General Electric X-Ray Corporation, Boston, Mass.
Hartford Accident & Indemnity Co., G. Allen Putnam, Agency, Manchester, N. H.
H. P. Hood & Sons, Manchester, N. H.
Horlick's Malted Milk Corporation, Racine, Wis.
Lederle Laboratories, Inc., New York, N. Y.
Lepel High Frequency Laboratories, Inc., New York, N. Y.
E. F. Mahady Company, Boston, Mass.
E. H. Marcy Drug Company, Hillsborough, N. H.
Mead Johnson & Company, Evansville, Indiana.
Mellin's Food Company, Boston, Mass.
M. & R. Dietetic Laboratories, Inc., Columbus, O.
Philip Morris & Company, Ltd., New York, N. Y.
The P. J. Noyes Company, Lancaster, N. H.
The E. L. Patch Company, Boston, Mass.
R. J. Strasenburgh Company, Pharmaceutical Chemists, Rochester, N. Y.
Surgeons' and Physicians' Supply Co., Boston.
Tailby-Nason Company, Boston, Mass.
Winthrop Chemical Co., Inc., New York, N. Y.

OFFICERS OF COUNTY SOCIETIES: 1936-1937

Belknap County

President: Laura G. Jacques, Tilton
Vice-President: Harry A. Cheney, Campton
Secretary-Treasurer: Clifton S. Abbott, Laconia
Delegates: Richard W. Robinson, Laconia; Raymond J. Turley, Meredith
Board of Censors: Lyall A. Middleton, Plymouth; Park R. Hoyt, Laconia; John R. Perley, Laconia.

Cheshire County

President: Walter F. Taylor, Keene
Vice-President: Frank M. Dinsmoor, Keene
Secretary-Treasurer: John J. Brosnahan, Keene
Delegates: Osmon H. Hubbard, Keene; Frank M. Dinsmoor, Keene
Board of Censors: Walter F. Taylor, Keene; Norris H. Robertson, Keene; George N. Barry, Troy

Coos County

President: Lewis C. Aldrich, Jefferson
Vice-President: Albert C. Johnston, Gorham
Secretary-Treasurer: Ralph N. Jones, Whitefield
Delegates: Richard E. Wilder, Whitefield; James A. Ferguson, Lancaster
Councilor: Richard E. Wilder, Whitefield
Board of Censors: Herbert E. Wilkinson, Berlin; James A. Ferguson, Lancaster; Paul A. Dumontier, Berlin

Grafton County

President: Ralph G. Perry, Wells River, Vt.
Vice-President: Kenneth Churchill, Lebanon
Secretary-Treasurer: Leslie K. Sycamore, Hanover
Councilor: Arthur T. Downing, Littleton
Delegates: Robert M. Deming, Glencliff; Leslie K. Sycamore, Hanover; Leslie E. McKinlay, North Haverhill
Board of Censors: John M. Page, Littleton; Arthur W. Burnham, Lebanon; Ralph E. Miller, Hanover

Hillsborough County

President: Henry H. Dearborn, Milford
Vice-President: Charles F. Nutter, Nashua
Secretary-Treasurer: Deering G. Smith, Nashua
Councilor: Timothy F. Rock, Nashua
Delegates: Charles H. Cutler, Peterborough; Roland J. Joyce, Nashua; Joseph E. Larochelle, Manchester; Deering G. Smith, Nashua; Clarence E. Dunbar, Manchester.
Board of Censors: Ezra A. Jones, Manchester; Philip McQuesten, Nashua; Harry M. Morse, Peterboro.

Merrimack County

President: Wallace H. Tarbell, Contoocook
Vice-President: Charles H. Parsons, Concord
Secretary-Treasurer: Warren H. Butterfield, Concord
Councilor: Henry H. Amsden, Concord
Delegates: James B. Woodman, Franklin Falls; Henry H. Amsden, Concord; Warren H. Butterfield, Concord
Board of Censors: George M. Crowell, Suncook; Fred S. Eveleth, Concord; William P. Clough, New London

Rockingham County

President: Chester F. McGill, Portsmouth
Vice-President: Alice C. Lamphrey, Exeter
Secretary-Treasurer: Wendell P. Clare, Portsmouth
Delegates: Lawrence R. Hazzard, Portsmouth; Oscar B. Gilbert, Exeter
Board of Censors: Ralph H. Barker, Derry; Thomas W. Luce, Portsmouth; Donald W. Leonard, Exeter

Strafford County

President: Edward G. Marcotte, Dover
Vice-President: Albert E. Barcomb, Farmington
Secretary-Treasurer: Edna Walck, Dover
Delegates: Jeremiah J. Morin, Rochester; Harry O. Chesley, Dover

Sullivan County

President: Donald C. Moriarty, Newport.
Vice-President: Emery M. Fitch, Claremont.
Secretary-Treasurer: Henry C. Sanders, Jr., Claremont.
Councilor: Emery M. Fitch, Claremont.
Delegates: Henry C. Sanders, Jr., Claremont; Donald C. Moriarty, Newport.
Board of Censors: Ernest L. Huse, Meriden; John H. Munro, Sunapee; Robert H. Brooks, Claremont.

Clinics

The State Board of Health, Division of Maternity, Infancy and Child Hygiene is sponsoring a Maternity Clinic at the Laconia Hospital the third Wednesday of each month for expectant mothers who are not under the care of a physician. Miss V. M. Jennings of Lakeport is the nurse in charge of the clinic.

Four Tuberculosis Clinics have been started recently in Cheshire County. Dr. Robert B. Kerr of Manchester will be the examining physician with Mrs. Mildred Aiken, County Tuberculosis Nurse, assisting.

An appeal for more persons in Cheshire County to take advantage of the free Cancer Clinics being conducted at the Elliot Community Hospital has been made by Dr. Walter H. Lacey, examining physician of Keene. The State Legislature appropriated a sum of money for this work at its last session.

The State Cancer Commission reports that since establishment of eleven clinics the first of January, 1934, doctors attached to the clinics have examined 1,152 patients. Of this number, diagnosis showed that 39 per cent of those examined had cancer and treatment was prescribed.

Nurses

Miss Maude Miles, Superintendent of the New Hampshire Memorial Hospital, has recently resigned her position. Miss Miles plans to study this summer.

The District Nursing Association and Portsmouth Red Cross are making plans to have a course in home nursing, classes to be held at the Portsmouth Hospital under the supervision of Miss Velma Pettiner, R.N. The course will consist of twenty hours and will include such subjects as healthful home environments, care of the sickroom and patients, and feeding of the sick.

The New Hampshire Graduate Nurses' Association held its quarterly meeting in Concord March 11, with Miss Ruth Whitcomb, R.N., of Concord as Program Chairman. Miss Claribel A. Wheeler, R.N., of New York City, Executive Secretary of the National League of Nursing Education, spoke at both morning and afternoon sessions. Miss Wheeler addressed the Association on "Curriculum as it Affects State Groups." Miss Margaret Riley, head of the Dermatology Department at the Massachusetts General Hospital, spoke to the Public Health section and Miss Alice E. Jackson, Executive Secretary of the

Family Welfare Society, spoke to the Private Duty group.

Hospitals

The Laconia Hospital has recently acquired, from one of its prominent physicians, a McKesson Electric Oxygen Tent with which to treat pneumonia.

Personals

Governor H. Styles Bridges proclaimed Friday, May 1, as Child Health Day. The slogan chosen for this year was "Health and Security for Every Child." In proclaiming this day as Child Health Day, the Governor asked each community to take thought for its own needs and how they may be supplied and to give active and loyal support to the leadership in this regard of the Division of Maternity and Infancy of our State Health Department.

Dr. Anna Philbrook of the State Hospital in Concord spoke before the members of the Legion Auxiliary at Laconia April 15. Dr. Philbrook's subject was "Child Welfare."

The Spring meeting of the New Hampshire Surgical Club was held at the Laconia Hospital on April 22. The morning session was devoted to a Dry Clinic. Luncheon was served at noon. Fifty-four members were present. Dr. Mark H. Rogers of Boston addressed the Club on "Painful Shoulders" and Dr. Otto J. Hermann of Boston spoke on "Compound Fracture Therapy."

DEATHS

CONNOR—Harold J. Connor, M.D., aged forty-five, one of the leading physicians of Concord and a member of the staffs of the Margaret Pillsbury and Memorial Hospitals, died at his home, 41 Auburn Street, on April 8, 1936. He had been ill for several weeks and his death was directly due to cerebral embolus.

Born in Woodstock, N. B., he received his medical training at Tufts College Medical School, class of 1914. On August 5, 1917, he entered the military service, enlisting in the National Guard Medical Corps and was stationed both at Salem and Boxford, Mass. He served in France from September 23, 1917 to April 4, 1919. At various times he was attached to the 101st Engineers, the 102nd Field Artillery and the 103rd Infantry and was discharged on April 28, 1919. He started his service as a first lieutenant and on September 16, 1918 was promoted to a captaincy.

Dr. Connor was married to Miss Mary Cragg, of Concord, who survives him as do two children, Mary Louise and James.

BROOKS—Harlow Brooks, M.D. Word has been received of the death in New York City, April 13, 1936 of Dr. Harlow Brooks, internationally known as a diagnostician, and a summer resident of New Hampshire for several years. He was sixty-five years old.

Dr. Brooks, who was in great demand as a consulting physician and who numbered among his patients General John J. Pershing, Gerard Swope and Bishop William T. Manning, was stricken the Thursday preceding his death, following his return to New York from Florida.

Dr. Brooks was the guest speaker at one of the annual meetings of the New Hampshire Medical Society several years ago. For the past thirty years, he had maintained a home in Raymond to which he returned for week-ends and occasional weeks during the summer.

Dr. Brooks, who resided at 47 West Ninth Street, New York City, is survived by his widow, Mrs. Louise Davis Brooks, whom he married in 1899, and his daughter, Miss Ruth Brooks, who sailed for South America on April 2 with a scientific expedition.

NEW HAMPSHIRE STATE CANCER CONTROL*

Local control of the cancer problem requires the co-operation of a fairly large group of interested people, a trained and competent directing authority and a supply of money sufficient to defray the expenses necessary to attain the planned objective. While the group of interested people will consist of both physicians and laymen, it is obvious that the major policies of development and procedures should be directed by physicians.

In May 1931, an act (Laws of 1931, Chapter 146) entitled "An Act providing for state aid for persons suffering from cancer and for the creation and appointment of a Cancer Commission," was passed by the New Hampshire Legislature. This act provides in brief for a commission of five persons with the governor as ex-officio chairman and the four appointive members to consist of two laymen and two physicians. One physician shall be a member of the State Board of Health and one to represent the New Hampshire Medical Society. These appointees have no definite term but serve at the will of the governor and council.

The act further provides that the commission shall establish and support cancer clinics, make studies and surveys of the cancer situation in the state, expend money for clinical care and assistance of poor and indigent cancer patients, partly on a fifty-fifty basis with towns and counties, and partly outright. The commission may receive voluntary contributions for general or special purposes.

In visualizing the commission activities one must remember that New Hampshire is a small state with less than 500,000 inhabitants and with more than fifty per cent of them in the southern half of the state. Our fiscal year begins July 1 and our first year's appropriation was for $15,000. All but $600 lapsed on account of inactivity. Since then the yearly appropriation has been from $20,000 to that for this year and next of $35,000 for each year.

The selection of the personnel of the commission was not completed until December, 1931. During 1932 a survey of the state was made in an effort to ascertain the available resources for hospitalization and treatment and the number of cancer patients treated during the previous year. The commission felt its way carefully, furnished aid to indigent patients through the facilities of the welfare department and in 1933 began to establish diagnostic clinics with the assistance of the established clinic or-

*Summary of paper read on March 7, 1936, in New York City, before the Officers and Directors of the American Society for the Control of Cancer, by George C. Wilkins, M.D., of Manchester, New Hampshire, member of the New Hampshire Cancer Commission.

ganizations of the state health department. By November 1, 1933, there had been established eleven diagnostic clinics in general hospitals throughout the state and in 1934 this number was increased to thirteen. In 1934 and 1935, 1152 patients were examined at these clinics and positive cancer found in 451, or 39 per cent.

In 1933 and 1934 the commission, through the welfare department, expended $16,623 for the care of terminal cases and for hospitalization of other indigent cases, and in 1935 there was expended $16,097.40 for this purpose. The diagnostic clinic expense is approximately $7,200 per year and the general administrative expense about $5,300.

In 1935 the commission, having acquired information and experience through the co-operation with other departments, took over the entire management and supervision of state cancer control. In January, 1935, the commission established three treatment centers, in Manchester (Elliot Hospital), Concord (Margaret Pillsbury Hospital), and Hanover (Mary Hitchcock Memorial Hospital). At these hospitals there are available surgery, deep therapy x-ray and radium. The commission purchased 200 milligrams of radium and has allotted it to these three hospitals in such proportion as to augment the existing supply to 200, 100 and 100 milligrams respectively in each of the three institutions designated for treatment. This radium is available for free treatment of indigent patients, but may be used on other patients.

The present set-up and activities of the commission, which have been and are being developed after two years of study and observation, are as follows:

(a) An office in the State House with one lay member of the commission acting as secretary, assisted by one female clerk.

(b) One field nurse who had been trained for several years in an active cancer treatment clinic. This nurse investigates all cases asking for aid and confers with county and town officials. She makes arrangements for hospitalization and nursing care of all indigent cases. She contacts each diagnostic clinic at regular intervals and follows up reluctant patients. It is expected that a general follow-up system will be developed soon.

(c) A comprehensive record of expenditures and an index of all cancer patients seen at clinics or cared for by the commission. A copy of clinic examinations is forwarded to this office for filing. A report of all radium and x-ray treatments at the treatment centers is also sent each month.

(d) A monthly meeting of all members of the commission.

The activities carried on are divided into four fields of work.

1. *Conduct and Development of the Diagnostic Clinics.* This plan contemplates not only the examinations of patients presenting themselves at the clinics, but definite encouragement is given each clinic group to learn more about cancer, and to become more proficient in diagnosis. The greatly increased number of biopsies sent to the State Pathological Laboratory during the past two years attests to this increased efficiency. Physicians are invited to attend the clinics and are especially urged to accompany their patients. Closely related to diagnostic clinics are the three treatment centers, each of these centers being also one of the thirteen diagnostic clinics. In these three centers the number of operations for cancer during 1935 has not been ascertained but 410 radium treatments were given to 277 patients. However, 370 of the radium treatments were given at the Elliot Hospital in Manchester. In addition to the three treatment centers there are two other hospitals in the state, the Laconia Hospital and the Notre Dame Hospital in Manchester, that have deep therapy machines and competent radiologists. This makes a total of five hospitals where deep therapy may be given. Four hundred and sixty-nine series of deep therapy x-ray treatments were given to 355 patients in New Hampshire during 1935.

   Each fall the Cancer Commission, the directors of the clinics, the pathologists and radiologists have an all-day conference and annually the radiologists meet for a separate conference.

2. *The Care of Poor Cancer Patients.* This includes investigation, transportation to hospitals for treatment, remunerating hospitals for board, care and treatment, placing terminal patients in nursing homes when necessary and supplying nursing and medical care. The commission pays all of the expenses for such care but is reimbursed for fifty per cent of the expenses by towns and counties when these patients are receiving public money for support. In addition to this class of patients, the commission may give the same assistance to unfortunate persons who are trying to pay their own way and are not able to assume the added expense of cancer care and treatment. Money expended on this latter class of patients comes entirely from the commission funds.

3. *Accumulation of Records,* from which may be deduced statistics of importance regarding the cancer situation in New Hampshire. The New Hampshire State Board of Health has contributed much assistance from its vital statistics department and also by ruling in 1935 that cancer be a reportable disease.

4. *Education.* Pamphlets are distributed at each clinic. All requests from clubs for speakers have been supplied. Numerous articles regarding cancer, and emanating from the Cancer Commission, have appeared in local papers. Since December 10, 1935, there have been weekly broadcasts, thirteen in all, on various phases of cancer education and information, sent out over Station WFEA in Manchester. These broadcasts, either complete or in abstract, have been printed weekly in sixty newspapers. Mimeographed copies of these broadcasts have been prepared and have been mailed in answer to requests. The commission is cooperating with the American Society for the Control of Cancer in the preparation of a state-wide educational campaign.

Owing to the fact that New Hampshire is such a healthful state to live in, we have a larger proportion of elderly people and to this fact is probably due the high incidence of cancer within the state. In spite of this handicap, the commission hopes to reduce this incidence in the next few years. The commission takes considerable pride in the fact that of

the 112 cancer clinics in general hospitals approved by the American College of Surgeons in the United States and Canada, the Elliot Hospital in Manchester was included in the number, and of the forty-seven provisionally approved hospitals, the Margaret Pillsbury Hospital in Concord was included. The American College of Surgeons approved only thirty-three diagnostic cancer clinics and in this group seven of the New Hampshire clinics were listed.

NEW HAMPSHIRE MEDICAL SOCIETY

HANDBOOK OF THE EARLY SIGNS AND SYMPTOMS OF CANCER

Prepared by the Committee on the Control of Cancer, 1935

OBJECTS OF THE HANDBOOK

1. To furnish to the physician a summary of the available knowledge regarding the most important features of cancer, because if cancer is recognized in its *early stage*, and thoroughly and skillfully treated, the majority of these patients should get well; and in the more superficial group, such as the skin and lip, nearly all should get well.
2. To have at hand, a convenient abstract for reference, and as a reminder, so that no patient will lose the best chances for life.
3. To enlist the co-operation of every practitioner of medicine in a real effort to reduce the deaths from cancer by curing the early cancer, or the precancerous conditions.
4. To remind all physicians that a thorough physical examination on the patient's birthday, and better, each six months, will enable him to recognize many early cancers, or precancerous conditions that are now being neglected by the patient.

Committee on Control of Cancer
GEORGE C. WILKINS, M.D., *Chairman*,
HOWARD N. KINGSFORD, M.D.,
GEORGE F. DWINELL, M.D., *Secretary*.

CANCER OF THE SKIN

Cancer of the skin usually begins as a small, painless scaly thickening, or papule, associated with crusts which are likely to fall off and then recur. This is followed by a warty or papillary growth, associated with slight induration. It may then ulcerate, with the development of hard everted edges, and a granulating base, covered with crusts, the removal of which causes slight bleeding.

Cancer of the skin may begin as a small, flat, depressed thickening, which ulcerates and enlarges.

Cancer of the skin may begin as a "small pimple," with persistent ulceration, and absence of inflammation.

It may begin as a cutaneous horn, or may develop in a fissure, or in the scar of an old burn.

Benign warts if irritated may become malignant.

A mole or wart, especially if increasing in size, or beginning to form crusts or beginning to bleed, must be thoroughly treated at once. Bluish black moles are especially dangerous because of the likelihood of metastasis, and all of these should be removed by wide excision.

Cancer of the skin may be single, or is likely to be multiple in old people, who have senile keratoses.

Removal by excision, electrocoagulation, or irradiation should be done at once and completely. Caustic applications are dangerous.

CANCER OF THE BREAST

Cancer is one of the most common new growths of the female breast, most likely to occur about the time of the menopause, but may be seen in women of eighteen to thirty and in the very old. It is not uncommon to find the growth in unmarried women. About 1 per cent occur in men.

The growth appears insidiously and usually is found by accident while bathing or drying the skin. It may be found in any part of the breast. Absence of pain in the early cases is the rule, although darting pain may occur.

The presence or absence of a tumor is determined by examining the breast with the flat hand with the patient in both the sitting and in the recumbent posture. The characteristics of the tumor are best obtained by placing the patient in the recumbent posture, stripped to the waist, and while gently fixing the tumor with the thumb and index finger of one hand, the tumor is examined with the index finger of the other hand. The least possible manipulation should be made and with the greatest gentleness. Every solid tumor in a woman should be looked upon as malignant, until proved benign.

Early cancer of the breast usually appears as a single, hard, irregular, painless lump. Its hard consistency may be masked by overlying fatty tissue. It may coexist with benign tumors and chronic cystic mastitis; therefore multiple tumors often lead to an erroneous diagnosis. An attempt to lift the skin over the tumor may cause dimpling, or depression. Bloody discharge from the nipple may be of diagnostic import and should be carefully investigated. It may be due to a duct papilloma or a duct cancer.

All detectable cancers are fixed in the breast tissue; fixation to the skin or to the fascia of the pectoral muscle indicates advanced or late lesions. A visible tumor, retraction of the nipple, deformity of the breast, or ulceration of the skin suggests *late cancer*.

Hard, painless, discrete axillary nodes are confirmatory of advanced cancer; the absence of nodes does not negative the diagnosis although it indicates a more favorable prognosis. Transillumination of the breast with an appropriate light in a darkened room, or an x-ray of the breast and axilla by a competent roentgenologist, will be of aid in the diagnosis of breast tumors. According to our present knowledge, cancer of the breast is best treated by radical amputation and irradiation. Rapidly growing cancers in young people, far-advanced cases and those which have metastasized to distant parts, such as the lungs and the bones, should rarely be operated upon except for the palliative removal of a large, ulcerating and foul growth.

Every suspected breast tumor should be freely excised and examined clinically and microscopically. No physician should "wait for developments" or tell the patient to "not bother it until it bothers you". Tumors of the breast should not be rubbed or massaged.

CANCER OF THE LIP

Precancerous and cancerous lesions of the lip may result from excessive smoking, biting the lip; or excessive exposure to the sun, wind, or cold, over long periods of time, such as occurs in farmers and sailors. Chronic dental infection is one of the most frequent causes.

Cancer of the lip may begin as a "fever blister", or a superficial crust, fissure, ulcer, or wart, which may seem so simple to the patient that cancer does not enter his thoughts. Very similar lesions may have been present and may have disappeared earlier in life, leading the patient to expect lesions at an older age to disappear also.

The important lesson to learn is that if a lesion of the lip does not show signs of disappearance within ten days or two weeks, it should be regarded as cancer until proved otherwise.

The most distinguishing feature of cancer, though not the earliest, is the indurated edge or border which is due to the infiltrating character of cancer.

With the knowledge now available, cancer of the lip like cancer of the skin, should be entirely eliminated.

Disease in this area can always be recognized in its earliest stage by the patient, because the slightest gross change can be felt by the patient's tongue and can be seen in the mirror. In this early stage practically all cancers of the lip can be cured if treated skillfully and thoroughly at the beginning. Failures are due to delay, inefficient treatment, or to the application of some superficial irritating substance which causes congestion and increases the rate of growth. Silver nitrate or other escharotics should never be applied to questionable growths or ulcers.

CANCER OF THE MOUTH

Cancer in the mouth as elsewhere in the body can be cured in the early stages. It can be seen and felt by the patient and the physician, and, therefore, the diagnosis can always be made early, and thorough, skillful treatment should be applied at once.

It is primarily a disease of elderly people but may occur in infants and children. It follows local irritation, leukoplakia, or syphilis, but may occur without any of these causes being recognized. The association with syphilis makes the prognosis less favorable.

Chancres can be differentiated by finding the spirochetes. Gummas may be differentiated by biopsy. Cancer may occur associated with either of these lesions. A positive Wassermann test does not exclude cancer, should not delay treatment, and a biopsy should be done.

The early symptoms or signs are ulcer, induration, leukoplakia, with or without pain. The most common locations observed are the floor of the mouth, tongue, buccal surface of the cheek, soft palate and on the alveolar mucous membranes.

To make the diagnosis is often difficult and commonly requires consultation. Each case is a law unto itself. The treatment cannot be standardized. The final outcome is dependent on the judgment used in planning the first attack upon the disease, and the plan will depend much upon the extent of the disease.

CANCER OF THE LARYNX AND PHARYNX

The early symptoms are beginning hoarseness and local discomfort. The local discomfort may consist of a sticking sensation or a feeling of lump and tenderness during swallowing and frequently during phonation. If the vocal cords are involved, hoarseness is an early persistent symptom. If the growth does not involve the cords or is extrinsic, hoarseness will be a late symptom.

The symptoms depend on the location and upon whether the lesion is an induration or ulceration or both.

The responsibility of the physician lies in making an early diagnosis. In the event of suggestive symptoms developing; the patient should be examined by a laryngologist experienced in detecting tumors and making biopsies. Repeated examinations are frequently necessary in early cases before diagnosis can be positive. The treatment is by surgical means, laryngofissure or laryngotomy, or by irradiation, or both. Laryngeal cancer metastasizes fairly early and patients should be examined frequently for the appearance of cervical nodes.

CANCER OF THE LUNG

Cancer of the lungs or pleura is usually a metastatic growth from cancer elsewhere, but it may be primary. The earliest symptoms are cough and thoracic discomfort. If the pleura is involved, dyspnea due to fluid in the pleural cavity develops rapidly. The cough is frequently persistent and usually without expectoration unless it becomes bloody.

The diagnosis can usually be made early by x-ray examination. The treatment is palliative.

CANCER OF THE STOMACH

Of all the growths in the human body, carcinoma of the stomach is probably the most fatal and is probably the commonest of the internal cancers. One of the chief causes for error in diagnosis is failure of the attending physician to suspect its presence.

It is essentially a disease of middle life, i.e., between forty and sixty years of age, rare, but highly malignant in the thirties.

In most of the cases, premonitory symptoms are either slight or absent.

There is no one striking symptom or group of symptoms by which it can be recognized as such in the early stages.

The discomforts of the patient are commonplace, differing in no respect from indigestion, which can be accounted for by errors in diet, insufficient chewing of food, lack of teeth or dental infection, worry and overwork.

The diagnosis is difficult or impossible from the early symptoms alone, but these indefinite symptoms *that do not respond promptly to orainary intelligent medical and dietary treatment*, should suggest an immediate x-ray gastrointestinal examination which will usually determine the diagnosis.

The early indefinite digestive symptoms become associated with anorexia, occasional vomiting to relieve distress, slight pallor, loss of weight and finally constant pain and a palpable tumor. Unexplained secondary anemia, with fatigue, suggests gastrointestinal malignancy.

Of all diseases simulating carcinoma of the stomach, pernicious anemia and carcinoma of some other part of the gastrointestinal tract are the most confusing. Consideration of secondary symptoms and gastric ulcer may present problems in differential diagnosis.

In the early stages a palpable mass is not present and gross hemorrhage is rare at any stage. Vomiting is neither an early nor a characteristic symptom. Induced vomiting to relieve distress is not uncommon in later stages. Low acidity of gastric contents suggests cancer, though free acid may be present.

Any persistent or unexplained abdominal symptoms demand a careful gastrointestinal study especially by the x-rays.

The treatment is surgical, and only early diagnosis can make surgical procedures advisable or successful.

CANCER OF THE BOWEL

Of all the internal cancers, those of the bowel are most amenable to cure if the diagnosis is made at a reasonably early stage.

Cancer of the small intestine is comparatively rare, contributing only 2 per cent of the bowel cancers.

Of the remaining 98 per cent, about half are within six or eight inches of the anus, and the other half scattered throughout the colon.

The most important and earliest symptom indicating the possibility of bowel cancer is *the onset of*

increasing constipation where none existed before, or a definite and progressive increase in a previously mild constipation. Secondary symptoms may be colicky pain, gas and borborygmi, blood in the movements, loss of weight, secondary anemia and digestive symptoms.

Late symptoms are due to obstruction, metastases, loss of blood and toxic absorption. Alternating diarrhea and constipation, as well as constant diarrhea, are late symptoms. Complete obstruction may occur with remarkable suddenness. All cancers of the bowel ulcerate and as this frequently occurs early, a search for occult blood in the feces is a diagnostic procedure of great value. Blood and mucus in the stool are significant, though in cancer these constitute fairly late symptoms.

Any indication of the above picture should not be disregarded and a word of warning must be given regarding treatment. It is not only justifiable but advisable to investigate first, because in early bowel cancer it is possible so to ameliorate the symptoms by prescribing mineral oil and other medicines, that clinical improvement satisfactory to the patient occurs, while the growth itself is growing constantly, and constantly approaching the deadline of inoperability.

Reliable diagnostic measures are not difficult to apply and should always be used in the following order:

1. Digital examination of the rectum. Nine-tenths of all cancers of the rectum and therefore nearly one-half of all cancers of the bowel are within reach of the finger.
2. Examination of the lower bowel with the proctoscope and sigmoidoscope. This allows inspection of six inches more of the lower bowel, and also removal of biopsy specimens.
3. Barium enema and x-ray examination fluoroscopically. This observation is checked with plates. Note that in cases of suspected cancer of the bowel where a complete gastrointestinal examination is contemplated, the barium enema should be given first. Also methods (1) and (2) should be applied before any x-ray methods are instituted.

The treatment of carcinoma of the bowel is surgical. Only in some cases of cancer of the rectum is radiation helpful and then chiefly in palliation.

Many cures result from adequate surgical treatment of cancers of the rectum and colon, but this can occur only following early diagnosis.

CANCER OF THE UTERUS

Any woman who has a blood-tinted vaginal discharge, bleeding spells between periods or any type of bleeding after the menopause, should be examined with a very suspicious mind and all methods of diagnosis persisted in until accurate diagnosis has been made.

CERVIX

The earliest symptom is spotting, usually disregarded by the patient. Excessive bleeding occurs only after cauliflower growths or destructive ulceration has developed.

Diagnosis can usually be made by inspection of the cervix through a speculum and with good lighting. Ulcers, granulation tissue that bleeds freely after gentle wiping with a cotton swab, or productive growths are all suspicious local indications of early cancer. When there is deep ulceration with fixation of the cervix, or a large cauliflower growth, palpation alone will establish the diagnosis.

In early cases the diagnosis can be accurately made only by biopsy. The tissue should be removed from the edge of the ulcer or from the granulation tissue and placed in 10 per cent formalin solution.

Treatment of cancer of the cervix is by a combination of deep x-ray therapy and radium.

UTERINE FUNDUS

Early symptoms are either a watery blood-tinted discharge or bleeding from the uterus between periods or after the menopause. In fundus cancer the bleeding is usually in spurts, or at intervals, though it may become continuous particularly after the menopause.

These symptoms call for an immediate pelvic examination and an examination of the cervix. If the cervix and vagina are free from disease, a diagnostic curettage with pathological examination of the curettings must be insisted upon.

Diagnostic curettage should be performed under a general anesthetic and with aseptic precautions. The curettage should be gentle, but every part of the uterine cavity should be covered in order that no small area of malignancy may escape detection. All curettings should be dropped in 10 per cent formalin solution and sent to the pathologist.

The treatment of cancer of the uterine fundus may be surgical plus radiation, or radiation alone. This depends upon the duration of the disease, the mobility of the uterus and obesity or general condition of the patient.

DIAGNOSIS OF BONE CANCER

The early diagnosis of malignant bone tumors is dependent upon the following essential factors:

1. Malignant bone tumors may occur at any age.
2. Pain occurs early, even before swelling or deformity, localized directly to the point involved. That is, there is definite localized tenderness. This may be differentiated from arthritic pains by pain or tenderness appearing above or below the joint but not in the joint. It may be differentiated from neuritis by the absence of other neurological symptoms.
3. Swelling or deformity usually without but occasionally with pulsation.
4. *Roentgenographic examination. The final positive diagnosis is made only by an x-ray examination.* Sometimes an early lesion may require a second x-ray examination after a varying interval to determine its character. An early diagnosis of malignant bone disease may mean a cure.

Be suspicious, therefore, of: (1) all bone pains; (2) unexplained bone swelling; (3) atypical rheumatic pains.

CANCER OF THE BLADDER, PROSTATE AND KIDNEYS

1. *Hematuria is a danger signal at all times.* It is commonly due to a malignant condition of the urinary tract.
2. Painful, difficult and frequent urination demands a thorough examination.
3. Rectal examination of the prostate should be a routine procedure.
4. Cystoscopy and if necessary a pyelogram should always be used to establish and confirm the diagnosis.
5. Pneumocystograms are useful in outlining the growth and in determining the degree of induration.
6. Cancer of the bladder or kidney may occur at any age but rarely before the second decade.
7. Cancer of the prostate is rare before forty. It is, however, on the increase between the ages of forty and seventy.

INFORMATION ON BIOPSIES

The most accurate method for the diagnosis of malignancy is the microscopic examination of a portion of the tumor in the hands of an expert pathologist.

Details for performing biopsies vary with the individual situation; some are performed with the scalpel, others with the electric knife, some by one or another of several punches which are on the market, and some by curettage. In any case a living and not a necrotic part must be removed, preferably with a bit of the surrounding tissue. Merely clipping off the surface of a tumor is not adequate.

The best fixative is 10 per cent formalin solution. The tissue should be immediately placed in a volume about ten times as great as the mass of tissue removed.

The grading of tumors either for prognosis or radiation sensitivity is of academic interest but in some locations aids greatly in indicating the best method of treatment and the amount of irradiation to be used. When a malignant tumor is present, everything possible should be done to eradicate it, irrespective of histological grading.

Biopsy is of value in following the course of treatment—sometimes of critical value, and also, if properly done, it is harmless. Details of the history are of importance to the pathologist in all cases, but particularly in those in which physiological activities are likely to be superimposed in and around tumors such as menstrual hyperplasias in carcinoma of the uterus. Occasionally a clinical diagnosis of malignancy is not sustained by the microscopical picture, whereupon a consultation with the pathologist is imperative. A slight margin of disagreement in diagnosis between quickly made frozen sections and regular sections still exists. This disagreement is of immediate practical importance only if it concerns malignancy versus nonmalignancy and not if a mere name for a tumor or other condition is in question. Tissues, unless too dense, can usually be prepared in twenty-four to thirty-six hours, but the diagnosis is too serious for uncertainty to be present because of poor preparations.

To summarize: biopsies are harmless if done properly; they usually settle the diagnosis; but pieces of tissues must be properly chosen for this purpose. They are also necessary in many cases to follow the course of treatment. The pathologist can be depended upon to use methods of preparation of his materials to ensure the quickest reports consistent with the accuracy demanded.

There is more danger from massage or repeated manipulation in making examinations, especially in cancer of the breast, than in doing a biopsy.

ESTIMATES HOSPITALS HAVE LOST 35,000 EMPLOYES DURING THE DEPRESSION

Faced with a demand for services greater than at any time in their history America's hospitals, because of their financial condition, are being forced to function with a personnel reduced by 35,000, according to John Glossinger, vice-president of the Kny-Scheerer Corporation.

Mr. Glossinger bases his figure on a study made by the government of 6,112,529 cases on relief which revealed that in this number there were 20,000 who previously were hospital employes. Since the total number of United States unemployed is variously estimated as between ten and twelve million people, he said he believed that his 35,000 figure is conservatively correct.

The study brought to light one fact heartening to all friends of American public health, according to Mr. Glossinger. It proved that of over six million individuals on relief, only about fifty were physicians and surgeons. This compared with one thousand lawyers, three thousand ministers and religious workers and more than twenty thousand teachers.

Mr. Glossinger stated that May has brought two opportunities to hospitals to acquaint the general public with their work and with their needs. The first is National Hospital Day, observed on May 12, anniversary of the birth of Florence Nightingale, and the other is First Aid Week, which will be celebrated throughout the country May 17-23.

COMPULSORY HEALTH INSURANCE IN CANADA

Current reports in the newspapers are to the effect that British Columbia enacted a bill March 1, 1936, which requires participation in compulsory insurance against illness by wage workers receiving less than $1800 annually, except for farm workers.

Exemptions may be granted for domestic servants and certain other groups.

Contributions to the fund by employers are deducted from wages paid.

Benefits cover the wage earner, his wife and children, and include medical care by physicians, free public ward care in hospitals up to ten weeks, including obstetric service. Free laboratory service and diagnostic aids are provided and there is a cash maternity benefit for women who do not seek hospital accommodations.

Actuarial opinion was secured before the passage of the bill, but the plan is evidently on an experimental basis with the probability of adjustments to assure adaptability to conditions which may affect some features of the law.

The reactions to this law will be watched with interest in the United States.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 22201

PRESENTATION OF CASE

A forty-five year old American Negro pullman porter was admitted complaining of numbness and stiffness of the neck, shoulders, and both arms.

Two years before entry the patient, without previous injury, gradually developed stiffness and dull pain in the posterior cervical region radiating down both shoulders to the hands, particularly on the right side. The discomfort was progressive and damp weather caused some exacerbation. Several months after the onset he remained in a hospital for two months, during which time he was treated by means of baking lamps with considerable improvement. An x-ray at this time showed a "spot" in his spine which was said not to be tuberculosis. Thereafter he returned to work but the symptoms again returned to their previous intensity and he was unable to continue with his work. A year before entry he went to another hospital where a biopsy of a neck gland was done. This was diagnosed as tuberculosis and after a four weeks' stay he was transferred to a tuberculosis sanatorium. He remained at this institution for about a month but became dissatisfied with his treatment and was therefore referred to another sanatorium. Here, after remaining on a tuberculosis ward for sixteen days he was informed that he did not have tuberculosis and was placed upon a general ward. He remained there for five months, during which period he developed anorexia and steadily lost weight. He returned home three and a half months before admission to this hospital. At about this time the pain in his neck gradually subsided and in its place there appeared a sensation of "numbness and pins and needles", especially down the right arm and on the anterior abdominal wall. Since the onset he had lost about seventy-five pounds in weight and a proportionate amount of strength. For two months there was a cough productive of small amounts of white tenacious sputum, more marked in the morning. There was no blood streaking. He had no night sweats but often felt quite hot at night. There had been two attacks of "pleurisy"—one lasting for six weeks at the onset of his illness and another in the left chest continuing only for several days, nine months before entry. Up to a month and a half prior to admission the patient was ambulatory part of the time although there was some dyspnea with exertion. Thereafter he remained constantly in bed and became nervous, irritable, and slept poorly. Two days ago he became very weak and feverish.

Seventeen years before admission he had a persistent cold and for two weeks was confined to bed with rheumatism in the back.

Physical examination showed a well-developed but thin, weak man who appeared chronically ill. The skin was warm and dry and over the lower end of the sacrum there was an early pressure sore. Oral hygiene was poor and the pharynx, which was examined with difficulty, appeared negative. There was a 2.5 centimeter crusted wound just posterior to the right sternomastoid muscle. This was slightly tender and a small amount of yellowish pus was expressed from it. A walnut-sized, firm, fixed, nontender mass was palpated just below the right mastoid process and several firm bean-sized nodes were present in the posterior cervical region. There was marked limitation of motion of the spine in all directions in the cervical and dorsal regions. Only slight tenderness was elicited over the upper cervical region, but there was marked spasm of all the neck muscles posteriorly. There was slight scoliosis to the right in the lower cervical and upper dorsal regions. Much wasting of the chest and shoulder girdle muscles was noted. There was markedly limited expansion of the chest bilaterally. A soft, fluctuant, slightly tender mass, measuring 10 by 8 centimeters, was found over the lower right scapula. The lungs were clear. The heart was normal. The blood pressure was 80/50. There was slight spasm and tenderness in the region of the left rectus muscle, most marked just below the umbilicus. No masses were felt. There was wasting and weakness of all the extremities, especially of the right arm, and finger flexion was limited on this side. Deep tendon reflexes were active but slightly exaggerated in the left upper extremity. There was no Kernig sign but a right hand and a questionable left Babinski sign were elicited. Sustained ankle clonus was observed on the right.

The temperature was 99°, the pulse 120. The respirations were 30.

Examination of the urine was negative. No Bence-Jones protein was found. Examination of the blood showed a red cell count of 3,800,000, with a hemoglobin of 70 per cent. The white cell count was 8,500, 88 per cent polymorphonuclears. Repeated sputa examinations were negative for tubercle bacilli. Stool examinations were negative. A Hinton test was neg-

ative. The serum protein was 5.2 grams per cent. The serum calcium was 8.5 milligrams per cent and the phosphorus 3 milligrams per cent. Creamy pus obtained from the abscess cavity on the back on one occasion showed four acid-fast bacilli. An intradermal injection of 1:10,000 tuberculin showed a one centimeter erythematous area with a raised center after forty-eight hours.

An x-ray showed the left diaphragm to be higher than the right and the lung markings were increased particularly on the right side. There was a slight lobulated widening of the supracardiac shadow. The heart and liver were not enlarged. The spleen was not seen. There was a small area of bone absorption near the vertebral end of the right first rib, destruction of the anterior and right lateral portions of the eighth dorsal vertebra, and an area of destruction in the fourth dorsal vertebra. There was a large soft tissue mass about the eighth dorsal vertebra, and a well-defined area of destruction in the left eleventh rib with a pathological fracture. The skull was negative. There were fleck-like areas of destruction in the middle thirds of both humeri and areas of destruction in the left side of the sacrum and wing of the ilium, the left ischium and right transverse process of the fourth lumbar vertebra. Films a week later showed a compression fracture of the second dorsal vertebra on the right side, an area of destruction of the second vertebra and a large soft tissue mass between the spine and pharynx extending from the base of the skull to the fifth dorsal vertebra. There were now multiple small shadows throughout both lung fields with widening of the superior mediastinum, more prominently on the right.

The patient's temperature fluctuated between 98° and 103° and his pulse between 90 and 130. He became progressively weaker, developed considerable difficulty in swallowing, and died on the twenty-second hospital day.

Differential Diagnosis

Dr. William B. Breed: Now to go back over the history, we can discard at once any of the benign affairs of the back such as arthritis or rheumatism of various sorts, because as we read through the whole history we know this is a mortal disease and we must consider, therefore, mortal diseases. There is conflicting evidence; first he had tuberculosis and then he did not; then he had it, and then he did not. That history it seems to me makes one at least suspicious of tuberculosis. By that I mean there was enough evidence for such a diagnosis early in the disease to have him spend a good deal of time in a tuberculosis sanatorium. He had symptoms referable to some lesions in the spine with nerve root irritation which apparently progressed, and later on he was found to have abscesses presumably emanating from the spine through the neck, perhaps retroperitoneally, and into the mediastinum. The appearance of the bones and ribs by x-ray is very confusing to me, and I think it throws me off a good deal from the diagnosis of tuberculosis. But if we leave the x-ray out, in a differential diagnosis tuberculosis must come first. I believe we can very easily rule out myeloma for two reasons. Bence-Jones protein is absent in the urine and the serum protein is not elevated. I hope we shall hear something interesting from Dr. Hampton about the x-rays.

Metastatic carcinoma might perfectly well cause this x-ray picture and I am not familiar with such an appearance caused by tuberculosis. These calcium and phosphorus figures were put in, I suppose, either to substantiate or eliminate some disturbance in the parathyroid because of the x-ray picture; but certainly there is no evidence of that. There is a low calcium and a normal phosphorus level which does not mean anything except possible debility and general cachexia before death.

I approached two x-ray men in this hospital and asked them if they recognized tuberculous osteomyelitis. I personally have not seen actual pathologic fractures and destruction of bone on the basis of tuberculous osteomyelitis. They said, "I am sorry but I cannot talk to you because I know about this case." So I ran away. Now I am wondering whether there is anyone here who can give me an unprejudiced opinion on this x-ray. If Dr. Hampton knows about this case I do not want to hear anything from him unless he can refrain from giving the show away.

Dr. Aubrey O. Hampton: I will tell you what I said about the case before I did know.

The patient is a Negro. That is one of the important points of the x-ray examination and furthermore he has these lesions that were described in the report as multiple areas of bone destruction. Here is one in the rib. Here is a soft tissue mass surrounding the eighth dorsal vertebra which shows bone destruction. There is also bone destruction in the anterior body of the third cervical. Here is the trachea and larynx pushed forward by a huge retropharyngeal mass. I think you can see the extension of that swelling down to the ninth dorsal vertebra.

Dr. Breed: That can perfectly well be a cold abscess?

Dr. Hampton: Yes. They do produce destruction of the anterior margins of the vertebrae without destroying the joints occasionally.

Dr. Breed: How do you explain the pathologic fractures of the ribs and the lesions in the middle of the humeri?

Dr. Hampton: There is destruction of the vertebral margin of a rib including the pedicle of the vertebra. The pedicle, the transverse

processes and even a part of the laminae in the region of the second and third dorsal vertebrae have been destroyed. Here is the transverse process of the fourth lumbar vertebra, or what is left of it; it is also destroyed. This lesion here is probably the fracture in the rib that is described and it has united. I think you can see there the displacement of the trachea forward by the retropharyngeal mass.

DR. BREED: It says that there were fleck-like areas of destruction in the middle thirds of both humeri and areas of destruction in the left side of the sacrum and wing of the ilium.

DR. HAMPTON: I think that was bone atrophy as far as I can tell from this hasty examination. He had this lesion which may well have involved a portion of the brachial plexus and you would expect to get diffuse atrophy which would produce a fleck-like atrophy of the humerus.

DR. BREED: But not destruction?

DR. HAMPTON: I cannot be sure of that.

He also had something described in the upper end of the left femur here. He has atrophy in the upper end of the left femur, so I do not know that that is actually an area of bone destruction. I do not believe it is.

A PHYSICIAN: What about that left sacroiliac joint?

DR. HAMPTON: He has atrophy of the whole side of the pelvis and this is exaggerated but there certainly appears to be destruction there.

DR. BREED: It says here "areas of destruction in the left side of the sacrum and wing of the ilium".

DR. HAMPTON: I think this is the area described. It is not so obvious as some of the others.

There was a note which was rather inaccurate in the record and I think we owe a clarification of this to Dr. Breed. It says "a week later there were multiple small shadows through both lung fields with widening of the superior mediastinum, more prominently on the right". That is not quite accurate. They are more than multiple, they are numerous, and very fine and rather dust-like in appearance, not miliary exactly because they are smaller than the usual miliary lesion.

DR. BREED: I do not want to ask you to do any more interpreting than you feel like doing.

DR. HAMPTON: I was shown all of these films, all except the chest, and I asked if the man was a Negro. I was told that he was, and it was from this information that I was able to make the diagnosis. I do not know whether I should tell you exactly what it was. I said that this x-ray appearance can be due to this disease in Negroes, Chinamen and Scotchmen.

DR. BREED: I appreciate that. I shall have to ask you about that later.

Of course, the question comes down here as to whether we have to make one diagnosis or two and whether the whole thing can be explained on the basis of tuberculosis, which I think he had. There is a good deal of evidence for it: the past history seventeen years previously of persistent cough and "rheumatism" in the back, and the story of progressive spinal lesions which are confirmed by the appearance of abscesses, and nerve root pain and soft tissue masses in the mediastinum. The thing of course that defeats me a little bit is this appearance of destruction of the ribs, this moth-eaten appearance and the pathologic fractures, on the basis of tuberculosis alone.

DR. HAMPTON: There was one other error in the x-ray interpretation. The record spoke of an increase in the mediastinal shadow, but we have already explained the shadow as being paravertebral. It is not the mediastinum except as it occurs behind the trachea.

DR. BREED: It is a soft tissue mass that can perfectly well be a cold abscess from the spine. I hesitate to add any other diagnosis. Of course metastatic carcinoma will produce the picture in the ribs and in the other bones but we have no other evidence for it. He may have another disease but I think I shall be bold and attribute all the symptoms and signs to one disease—tuberculosis.

DR. TRACY B. MALLORY: Are there any other suggestions? Dr. Cave, what would an orthopedic surgeon think about it?

DR. EDWIN F. CAVE: I think it is the characteristic appearance of tuberculosis and the history and x-ray findings are both consistent with it. I think it is interesting that no joint is involved. It is purely a lesion of bone and not of the joints. You usually think of tuberculosis as being a joint affair as much as a skeletal one. I think I should agree with Dr. Breed that the diagnosis is tuberculosis and nothing else.

DR. MALLORY: Dr. Bock, you actually saw the patient; will you give your impression?

DR. ARLIE V. BOCK: We felt exactly as Dr. Breed did, that the bone lesions were not characteristic of tuberculosis, in spite of what Dr. Cave says, that they were more consistent with the picture that one might have from such a condition as metastatic carcinoma. Against that, however, was the very obvious retropharyngeal abscess extending down into the chest giving him increasing difficulty in swallowing, a condition that we thought would be very unusual except as secondary to tuberculosis of the spine. We decided on this basis that the underlying condition must be tuberculosis, in spite of the queer appearance of the other x-ray findings. We finally felt that he had a miliary process. He reminded me very much of a patient in the Baker Memorial a few years ago who had a prolonged illness with fever and very little specific symptomatology. She had malaise, weakness and

fatigue unassociated with any febrile state. She had had x-rays of most of the skeleton and the x-ray department said she had widespread metastatic malignant disease. There had been no x-ray visualization of cervical spine though she gave a history of having distress on swallowing. The x-ray of the neck showed a lesion somewhat like the one in this case and she had a retropharyngeal abscess which had penetrated through the posterior mediastinum to the diaphragm, all due to tuberculosis; the x-ray picture in the bones generally was later interpreted as the result of atrophy from long bed confinement.

DR. GEORGE W. VAN GORDER: I happened to have seen this patient in consultation, and felt that if one looked at the x-ray picture alone, the most likely diagnosis would be metastatic carcinoma. You can pick out single lesions in the x-ray which are identical in appearance to metastatic carcinoma.

But when you look at the clinical picture and realize that these bone lesions are associated with cold abscess formation and that the patient has a large retropharyngeal abscess resulting from destruction of the cervical vertebrae, then I am sure most of us would favor the diagnosis of tuberculosis in preference to carcinoma. I was wondering if any lesion could produce these signs and symptoms, such as actinomycosis, because, as Dr. Bock has said, the lesions in the bone are not at all typical of tuberculosis since they affect the bodies of the vertebrae and the shafts of the ribs rather than joint structures. If it is tuberculosis, which seems most likely, it is certainly an atypical form of the disease.

DR. HAMPTON: I hoped that Dr. Van Gorder would tell you of his cases of bone tuberculosis occurring in the Chinese. We have had two other Negroes in this hospital with extensive bone tuberculosis similar to this case. Bone tuberculosis is common in Scotland. There is one other infectious disease which might produce this whole picture, coccidioidal granuloma and I think that if the patient had come from California we would have strongly suspected coccidioidal granuloma.

CLINICAL DIAGNOSIS

Tuberculosis of the spine, glands and lungs.

DR. WILLIAM B. BREED'S DIAGNOSES

Tuberculosis (miliary) of lungs, spine, ribs and long bones.

ANATOMIC DIAGNOSES

Tuberculosis of the spine, multiple foci.
Paravertebral and epidural abscesses, tuberculous.
Tuberculous pachymeningitis.
Tuberculous lymphadenitis, bronchial.
Tuberculous pericarditis with synechia.
Tuberculous myocarditis and endocarditis, right auricle.
Tuberculosis of the ribs.
Acute miliary tuberculosis, terminal.

PATHOLOGIC DISCUSSION

DR. MALLORY: We found at autopsy multiple tuberculous foci throughout the vertebral column. There were two cervical and three dorsal vertebrae, particularly severely involved with compression fractures, as you can see at the midpoint of the specimen there. In a great many areas pus seemed to be exuding from the vertebral column in all directions, front, back, and sides. Why there were symptoms of referred pain in some areas and not in others was rather difficult to guess from the autopsy, because it looked as though the great majority of the spinal nerves were involved. In the cervical spine there was a definite epidural abscess and the dorsal roots were bathed in pus.

The other interesting and entirely surprising feature of the autopsy, there was nothing in the clinical history to give a lead to. The pericardium was completely obliterated by an extensive tuberculous process, evidently direct invasion from a tracheobronchial lymph node. The process had first obliterated the pericardial space and then had actually invaded the wall of the heart, so that in the right auricle the tuberculous process passed completely through the musculature of the auricle and there was an actual tuberculous endocarditis, if you want to call it that, of the intima of the right auricle. There was finally a terminal generalized miliary tuberculosis. What the course of events was here, we were not able to determine from the autopsy. The lesions in the spine appeared as old as those that we found anywhere else in the body. There was no evidence of any primary tuberculous infection in the lung.

A PHYSICIAN: I should like to ask whether there was any adrenal involvement, and whether he had any evidence of amyloid disease?

DR. MALLORY: Neither. The adrenals queerly enough did not show miliary tubercles.

DR. GEORGE W. HOLMES: Can you tell whether the pericardial lesion was old or recent?

DR. MALLORY: It was fairly old undoubtedly.

A PHYSICIAN: Were the bones of the extremities x-rayed?

DR. MALLORY: No, we did not examine those. The ribs showed atypical tuberculosis.

DR. CAVE: Do you think the appearance of the vertebral bodies was due to intrinsic disease or to pressure from the abscess?

DR. MALLORY: Probably in part from both. Sections of the vertebral bodies showed older and younger tubercles scattered throughout and some of the lesions undoubtedly were primary

in the vertebra. On the other hand, the vertebrae behind the cold abscesses showed erosions of their anterior margins which I am sure were secondary.

CASE 22202

Presentation of Case

First Admission. A twenty-one year old Armenian dancing instructor was admitted complaining of jaundice and fever.

For two years the patient had had many bouts of fever persisting for two to four days and occurring at about two week intervals. At the onset, while still in Armenia, following a severe chill he had been treated in a hospital for what was said to be malaria. Soon after discharge he immigrated to this country. Since that time there were no chills but he had profuse perspiration following fever. He was not confined to bed during his febrile periods. Two weeks before entry he had an attack persisting for five days during which he first noticed the presence of jaundice. The icterus subsided with the pyrexia but recurred two days prior to entry when he again became feverish. His temperature had not been taken since his initial illness but he had taken quinine with each febrile spell. There was some anorexia but no abdominal discomfort, nausea, emesis, bowel irregularity or respiratory disturbance. He noted that his urine was reddish during each attack.

Physical examination showed a well-developed and nourished young man with a deep icteric tint of the skin and sclerae. The heart was normal. The blood pressure was 104/80. The lungs were clear. The abdomen was soft and the liver dullness extended from the sixth rib to a point just beneath the costal margin. The spleen was not palpable. No tenderness was elicited.

The temperature, pulse and respirations were normal.

Examination of the urine showed a specific gravity of 1.026 with a trace of albumin and a positive reaction for bile. The sediment was negative. Examination of the blood showed a white cell count of 7,800, 72 per cent polymorphonuclears. The hemoglobin was 85 per cent. The stools contained bile and examination showed no blood, pus, fat or parasites. A blood Wassermann test was negative.

X-ray examinations of the gallbladder region and teeth were reported as normal.

For a month after admission the patient remained afebrile. His jaundice gradually subsided except for a single exacerbation two and a half weeks after entry. On the thirty-sixth hospital day his temperature suddenly rose to 102.5° and the jaundice again became deeper. At this time the edge of the liver became palpable and was reported to be smooth and tender. The tip of the spleen was also felt. On two succeeding days he had an irregular fever fluctuating from 98° to 102°. Several times a severe chill preceded the rise in temperature. An echinococcus complement fixation test was negative at this time. Thereafter the temperature returned to normal and on the sixtieth hospital day a cholecystectomy and a choledochostomy were done. At operation the gallbladder was found to be thickened and this process was said to extend to the common duct. The liver was small and nodular. A probe was passed through the common duct into the duodenum without difficulty. Postoperatively the patient exhibited scanty drainage of bile but otherwise responded fairly well and was discharged on the eighty-second day. No note was made of the degree of jaundice at this time.

Second Admission, six years later.

Following his discharge the patient felt weak for several weeks and then gradually regained his strength. There was no recurrence of his fever, chills, or jaundice and he had no further symptoms until six months before re-entry. At this time he first noted that his abdomen was slightly more prominent than usual. This abdominal swelling progressed very gradually and three and a half months later he developed pain and swelling in the left ankle. This continued for about two months and then subsided spontaneously shortly before his readmission to the hospital. He had no symptoms referable to his gastrointestinal tract.

A brother had developed jaundice at approximately the same time as the patient, six years before. This persisted and, except for pruritus, was associated with no other symptoms. At the end of six months, the icterus having continued, the brother had a cholecystectomy performed. He responded poorly postoperatively and died one month later after a stormy febrile course.

Physical examination showed a poorly developed, fairly well nourished man in no discomfort. There was a questionable icteric tint to the sclerae. A few shotty nodes were palpated in the right axilla. The heart was not enlarged but a loud blowing systolic murmur was audible in the pulmonic area. The blood pressure was 92/50. Both sides of the chest were dull to percussion posteriorly up to the angles of the scapulae. Few coarse râles were audible at the angle of the right scapula. The abdomen was tender and rounded. Shifting dullness and a fluid wave were elicited. The liver dullness extended from the fourth interspace to a point two finger-breadths beneath the costal margin. The edge of the spleen extended two centimeters beneath the costal margin with inspiration.

The temperature, pulse and respirations were normal.

Examination of the urine was negative. The blood showed a red cell count of 3,280,000, with a hemoglobin of 65 per cent. The white cell

count was 3,250, 70 per cent polymorphonuclears. A stool examination was negative. A van den Bergh test gave an indirect reaction and showed 1.7 milligrams per cent of bilirubin. A red blood cell fragility test showed hemolysis beginning at 0.38 and complete at a saline dilution of 0.28. An icterus index was 5. A liver function test showed 5 per cent retention after thirty minutes.

With a low base diet, ammonium chloride and novasurol the patient developed an adequate diuresis, lost ten pounds and was relieved of his ascites. He was discharged on the fourteenth day.

Third Admission, seven and a half years later, at the age of thirty-five.

Following his last discharge the patient had slight swelling of his ankles for about two years and there was no evident recurrence of the abdominal swelling. Thereafter he remained symptom free until the morning of his re-entry. At this time he was awakened by an agonizing nonradiating pain in his right side just under his ribs. The pain was not increased by respiratory movement or walking. An enema produced no fecal return and shortly afterward he vomited about two cups of greenish material. This was followed by four brief but severe chills. He noted a slight burning dysuria. Four hours after the onset the attack ceased abruptly.

Physical examination showed a slightly emaciated pallid man in no discomfort. The tongue was smooth and pale and the pharynx was slightly injected. The heart was not enlarged. A soft systolic murmur was heard at the apex. The blood pressure was 120/50. The lungs were clear. The abdomen was slightly distended and shifting dullness was elicited in the flanks. Liver dullness extended from the fifth interspace to the costal margin. The spleen was moderately enlarged. Rectal examination showed the presence of external hemorrhoids.

The temperature was 100.5°, the pulse 90. The respirations were 25.

Examination of the urine showed a specific gravity of 1.012 with a slight trace of albumin. The sediment contained a few white blood cells and was loaded with red blood cells. The blood showed a red cell count of 3,030,000 with a hemoglobin of 60 per cent and a volume index of 1.16. The white cell count was 3,000. A van den Bergh test showed 3.15 milligrams per cent of bilirubin. A serum cholesterol was 150 milligrams per cent. The serum protein was 5.4 grams per cent. The nonprotein nitrogen of the blood was 24 milligrams per cent. A phenolsulphonephthalein test gave 85 per cent excretion at the end of one hour. The venous clotting time was nine to ten minutes. The liver function was recorded as 10 per cent.

X-ray examination showed the right kidney outlines to be normal. The left kidney was a little low in position and rather broad across its mid-portion. There was a crescentic area of calcification lying just to the right of the first lumbar vertebra and a second calcified area overlying the eleventh rib over its vertebral articulation. Except for thickening of the hilar shadows and a slightly heightened left diaphragm the chest was negative. Examination of the esophagus showed the presence of varices. An intravenous pyelogram showed prompt appearance of dye on both sides. There was an anomalous configuration of the left kidney. There was no evidence of stone. The calcified areas were evidently outside of the genitourinary tract.

The patient was treated palliatively and given parenteral liver extract. His temperature returned to normal on the second day and remained normal thereafter. The hematuria continued but lessened to 20 red blood cells per field. The patient was discharged on the ninth day.

Final Admission, two months later.

He returned to normal activity following his last discharge and four weeks before readmission he began to notice evening swelling of his ankles which was relieved by bed rest. A week later the ankle swelling persisted and his abdomen gradually became enlarged. This produced some generalized abdominal discomfort but no actual pain. Occasionally he had fleeting joint pains which were not associated with local swelling or redness. His appetite was good and his bowel movements were regular but pale yellow. His urine became scanty and dark brown in color.

Physical examination showed a slightly jaundiced, thin man in no discomfort. Dullness was elicited in both chests from the fourth ribs anteriorly and the angles of scapulae posteriorly to the bases. The breath sounds were absent here. The heart findings were not noted. The abdomen was tense, bulging, and the umbilicus pouted. There was edema of the penis and lower extremities.

The temperature was 98°, the pulse 110. The respirations were 25.

The urine contained a large amount of bile but the sediment was negative. The blood showed a red cell count of 3,570,000, with a hemoglobin of 75 per cent. The white cell count was 4,600. 91 per cent polymorphonuclears. The stools were greenish in color but otherwise negative. The blood cholesterol was 166 milligrams per cent and the serum protein 4.9 grams per cent. The van den Bergh showed 6.26 milligrams of bilirubin.

Three thousand cubic centimeters of clear amber fluid was removed by abdominal paracentesis. This showed a specific gravity of 1.010, a total protein of 0.8 grams per cent, and contained 2,260 cells per cubic millimeter, of which

2,000 were red blood cells. The patient was treated with intravenous glucose, repeated transfusions, mercurial diuretics, and abdominal taps with resultant diuresis of a moderate degree and a weight loss of twenty pounds. Several febrile episodes occurred, the first of which was associated with a tender, reddened swelling in the right Scarpa's triangle. Later râles appeared in the right axilla and subsequently there developed an area of dullness with bronchial breathing in this region. At the end of one month his temperature began to show a daily fluctuation between 98° and 100° with occasional rises to 103°. The serum bilirubin content remained unchanged at 6.85 milligrams per cent. On the forty-first hospital day the patient's temperature rose to 104° and on the following day a brawny indurated swelling appeared on the face and assumed a somewhat symmetrical butterfly appearance. The lesion spread peripherally and presented a rather sharp raised edge. The white blood cells rose to 15,000 and the temperature fluctuated between 99° and 105°. Thereafter he went rapidly downhill and died on the forty-fifth hospital day, fourteen years after his initial entry.

Differential Diagnosis

Dr. Wyman Richardson: The story on the first admission makes one think of paroxysmal hemoglobinuria, hemolytic jaundice, and biliary cirrhosis as possible diagnoses. We might add to that the possibility of quinine susceptibility in malaria, but as we go on I think there is very little evidence for the diagnosis of malaria.

"The abdomen was soft and the liver dullness extended from the sixth rib to a point just beneath the costal margin." The liver therefore does not appear to be large, if anything it is small. The spleen is not palpable, which is opposed to a diagnosis of hemolytic jaundice.

"Examination of the urine showed a positive reaction for bile." Bile, as such, would not be present in the urine from hemolytic jaundice. It is not an obstructive jaundice, however, as there is bile in the stool.

"A blood Wassermann test was negative." That is against a diagnosis of paroxysmal hemoglobinuria; also, the presence of bile in the urine against that diagnosis.

"At this time the edge of the liver became palpable and was reported to be smooth and tender." A large liver in hemolytic jaundice is also said to be quite rare.

One can question why operation was done. I assume that this patient probably had a biliary cirrhosis from the story thus far, and very likely they felt that the infection was coming from the biliary tract. The cholecystectomy with drainage of the biliary tract might help to overcome that infection. I cannot see any evidence for gallstones or any other disease that in itself requires operation. The findings at operation are not those of ordinary biliary cirrhosis which usually is associated with an enlarged liver.

"A brother had developed jaundice at approximately the same time as the patient, six years before." The problem is whether he had the same disease that the other brother had. As far as hemolytic jaundice goes, it may be familial, of course, but the story does not suggest hemolytic jaundice and I do not see how his brother had it. In regard to the familial incidence of infectious biliary cirrhosis I have a vague remembrance that it may occur in more than one member of the family but I cannot remember, nor can I find it in any common text.

I do not know how one can percuss liver dullness in an abdomen full of fluid. I am rather surprised at that. These symptoms that appear in the second admission, are the first ones of a beginning difficulty with circulation through the liver and a beginning cirrhotic liver.

"The white cell count was 3,250, with 70 per cent polymorphonuclears." With the leukopenia this is rather strange because it shows seventy per cent polymorphonuclears. Usually leukopenia is due to reduction in neutrophiles.

"A stool examination was negative." I take it that means there was bile in the stool.

The blood findings are not very characteristic of anything. The blood smear is not described. We assume he has a beginning cirrhotic process in the liver and it would be perfectly all right to explain the blood picture on that basis. Whether it is a macrocytic anemia or not is not stated.

"With a low base diet, ammonium chloride and novasurol the patient developed an adequate diuresis, lost ten pounds and was relieved of his ascites." That was about six or eight years ago. I remember about that time we found that you could produce a diuresis in cirrhosis of the liver by giving ammonium chloride and novasurol, or salyrgan.

It is a little difficult to explain that attack of pain on any other basis than on the basis of liver pain. Just what the mechanism of pain is in these cases, I do not understand; but we know one can get pain in catarrhal jaundice and in cirrhosis of the liver and other liver conditions without being able to explain the exact mechanism of the pain.

"The abdomen was slightly distended and shifting dullness was elicited in the flanks. Liver dullness extended from the fifth interspace to the costal margin." The liver seems to be shifting back and forth all the time.

"The sediment contained a few white blood cells and was loaded with red blood cells." You do occasionally get hematuria in cirrhosis of the

liver, at least in portal cirrhosis of the liver, and I am explaining the hematuria on the basis of liver disease.

The blood picture seems to be a macrocytic anemia now. The white count is 3,000. The picture is perfectly correct for pernicious anemia, also for advanced liver disease. The interesting thing about the anemia of liver disease, which sometimes looks like pernicious anemia, is that it is often very difficult to treat. One would think that advanced liver disease might destroy enough of the active principle so that these patients would develop pernicious-like anemia. However, if this were so why do they not respond to liver therapy?

X-ray Interpretation

Dr. George W. Holmes: There were many x-ray films, some are quite interesting. The films of the esophagus show considerable widening of the esophagus and some delay in the passage of barium through it, and the lines here, which show better in the smaller film, are quite characteristic of esophageal varices. Here is another film showing the worm-like lines of rather large varices. It is interesting that when the esophagus is full you cannot see them. They show much better when the esophagus is empty. The films taken of the stomach I think show rather prominent gastric rugae. As you would expect in this case, the stomach is high and empties rapidly into the small bowel.

In these films of the urinary tract you can see the outline of the left kidney here. It is a bit unusual for the left kidney to be lower than the right. The left kidney is larger and lower than the right and definitely abnormal in the upper pole. The kidney pelvis is displaced downward and outward. This shape of the kidney itself seems to be abnormal, as though there were a mass in the upper pole of the kidney.

Dr. Richardson: Could it be overlying spleen?

Dr. Holmes: No; I do not believe so. The spleen might push the kidney down and the small liver might allow the right kidney to be high; but I do not believe a large spleen would give you this shape or distort the kidney pelvis.

Here is the crescentic shadow described. It appears to be below and outside the kidney. I do not believe it is part of the kidney shadow.

This shadow at the eleventh rib could be due to calcification in the wall of an aneurysm. It seems to be constant and it is not part of the kidney.

We have a film of the chest which shows a relatively high diaphragm on the left. The heart shadow is slightly increased and the hilus vessels are prominent but there is nothing else.

A Physician: Is that calcified and elongated enough to call pathologic?

Dr. Holmes: No; I think it is more anatomical.

Differential Diagnosis Continued

Dr. Richardson: I have explained the calcified area as perhaps calcification in a hematoma resulting from the previous operation, although there was no evidence of hematoma at that time, and that is the way I am going to leave it. In regard to the kidney I am going to say it is a red herring and it is probably a congenital abnormality. Would that be consistent with the x-ray interpretation?

Dr. Holmes: That is a possibility.

Dr. Richardson: I am not going to pay any attention to it. We shall see later.

I have not paid any attention to the joint pains. I think it was a toxic reaction and partly due to swelling of the legs.

He has now, as you will see later, an increasingly low serum protein, so that he is perfectly entitled to edema anyway.

The problem of leukopenia in this patient, with cirrhosis of the liver, with large spleen is interesting. I do not know whether there is any definite relationship in these cases between the spleen and the leukopenia.

"The stools were greenish in color but otherwise negative." That is suggestive of biliary type of cirrhosis.

It is rather complicated working out everything here and I am going to stick to what I think was the essential disease this man had. He was a young man who lived for thirteen and a half years following his first attack of jaundice. I am going to rule out all rare tropical diseases. I do not know enough about them to talk about them; and it certainly is not malaria. He has recurring jaundice with fever, jaundice that is not obstructive and associated sometimes with greenish stools. He had splenomegaly and a long chronic history. These things spell to me infectious biliary cirrhosis. It is rare to get edema in biliary cirrhosis but I am sure as the process goes on you get secondary fibrosis and rarely a cirrhotic process in the liver. All the symptoms can be explained on that basis except possibly the hematuria and this question of the kidney. I am going to say it is not an important feature in this disease. I think he died of erysipelas. I think it is quite possible that Dr. Mallory will find acute vegetations on the valves of the heart, although there is not much evidence to go on there. Dr. Mallory is very much inclined to turn up a neoplasm in these cirrhosis cases but I do not believe he is going to this time. So that I will say he has biliary infectious cirrhosis with a terminal erysipelas and a question as to whether there may be a terminal acute septic endocarditis. I think

the calcification here was from an old hematoma. As to what the kidney is going to look like, I do not think I will say.

DR. TRACY B. MALLORY: I think perhaps we should have given Dr. Richardson one other piece of information which those of us who followed this patient all knew. The patient's brother died and was autopsied in this hospital nearly fifteen years ago, a few months after the onset of his illness. He showed a very atrophic, grossly nodular liver that could be described as either subacute atrophy or rather rapid cirrhosis. I do not know whether that makes him want to change his diagnosis.

DR. RICHARDSON: I am not going to say any more. I have said too much already.

DR. MALLORY: Dr. Jones, you followed this patient for fifteen years and know him better than anyone else.

DR. C. M. JONES: He represents a very unusual picture of chronic liver disease apparently starting with a clean cut attack of catarrhal jaundice, the brother developing the same type of hepatitis within a week. I have forgotten which came first. I believe this man was first and the brother a week later. Both of them were in the ward under the care of Dr. W. D. Smith at that time, and while on the ward the jaundice increased during the period of a month to two months. The feeling was that the symptoms were due to intrahepatic disease and that possibly if we could provide more adequate biliary drainage they might improve. I do not think we would perform the operation on a similar case now. It would be interesting to see what Dr. Vincent says. At that time we thought it wise, and in this particular instance operation was performed by Dr. Vincent and there was reduction in jaundice following that operation. The brother, who had an identical condition, was operated on I think four months after the onset. He went out of the hospital after his first admission and then returned for operation because he was getting worse, but the operation was followed by a relatively short survival period. At operation in each instance the liver showed what would appear to be grossly the results of a subacute yellow atrophy with regeneration. Both livers were nodular although the nodules were relatively small. This patient that we are discussing today was jaundiced for about a year, if I remember correctly, but it finally diminished until it no longer played a part in the picture. The next symptom of importance and what interested me most was the development of ascites and edema. He came in to see me because his feet were swollen, he could no longer give dancing lessons and it was obvious he had ascites. He was given a course with novasurol and was then free from ascites for many years. I think possibly that is the most important point to be gained from the discussion of this case. Here was an individual with chronic liver disease, undoubtedly infectious in origin, with liver damage and regeneration, who subsequently developed enough hepatic insufficiency so that he developed ascites. As a rule if we have edema with it when ascites develops it is pretty close to a terminal event. In this case following rest and adequate treatment with a diuretic his ascites disappeared not to recur for at least six years, when he came in again with swelling of the abdomen. I think it is increasingly true as we watch these cases that the prognosis is very difficult to make correctly, and even with marked ascites one can be more optimistic than statistics would have us believe. This man earned his living, following the disappearance of ascites, until a few weeks before he came into the hospital this winter. During the past three years one other symptom has been of some interest and that is, that he had a very intractable anemia. The red count for the most part had stayed in the low three millions and it was impossible with massive doses of iron to alter it very much. I think that spells a high degree of liver insufficiency with inadequate reformation of hemoglobin. In spite of that he was able to carry on until the terminal event; namely, return of ascites and edema, and subsequently an intercurrent infection which he could not resist.

There is a case on Ward E at the present moment which is of some interest. He is now going through exactly the same cycle, ascites and jaundice, and appeared to be recovering very satisfactorily until he picked up a streptococcus infection and erysipelas. He very nearly failed to survive it but is improving again at the present moment. It seems that these people with liver damage of any degree stand ordinary infections very poorly. The picture—Dr. Mallory will give us that—started with catarrhal jaundice. I think it is not fair to say infectious biliary cirrhosis because almost all liver changes that take place in relation to catarrhal jaundice are in the nature of acute yellow atrophy with regeneration leading to another type of cirrhosis, so-called toxic cirrhosis. I believe that is what he showed at autopsy.

DR. WILLIAM D. SMITH: I saw this man once thirteen years ago and strangely enough I remember him, probably because there were two of them. His brother was also a very interesting case. I remember that the feeling of the staff at that time was that he did have a biliary cirrhosis and although Dr. Vincent operated on him I remember Dr. Daniel Jones coming by on the ward and advising operation for exactly the same reason that Dr. Richardson gave this morning. Some cases of biliary cirrhosis with infection of the intrahepatic

ducts are questionably improved by drainage of the common ducts.

I do not believe we were thinking quite so much fifteen years ago about healed acute yellow atrophy and I think in view of what we know now, and in view of the fact that the liver of the first brother to be operated on was small and nodular, one would have to consider pretty seriously healed yellow atrophy or toxic cirrhosis with portal obstruction.

DR. BETH VINCENT: A number of years ago we explored a certain number of these infectious jaundice cases in the hope that if we found a lesion of the gallbladder we could remove it, institute drainage and favorably influence the course of the disease. Although this man lived a long time and had periods of good health we came to the conclusion that we had not accomplished anything in this case or in any of the other cases. We decided that it was not only a procedure without benefit but in certain of the cases it might be a procedure of very considerable risk; so we gave it up.

CLINICAL DIAGNOSES

Cirrhosis of the liver, cause undetermined.
Erysipelas of the face.

DR. WYMAN RICHARDSON'S DIAGNOSES

Infectious biliary cirrhosis of the liver.
Erysipelas.

ANATOMIC DIAGNOSES

Cirrhosis of the liver, toxic.
Ascites.
Esophageal varices.
Icterus of the skin, marked.
Erysipelas of the face.
Peritonitis, acute fibrinous (sterile).
Splenomegaly.
Pulmonary edema, bilateral.
Operative wounds: Cholecystectomy, old, and abdominal paracentesis.
Lymphadenopathy, retroperitoneal glands.
Ulceration of the stomach, slight.
Edema of the extremities, slight.

PATHOLOGIC DISCUSSION

DR. MALLORY: The autopsy on this man showed an atrophic liver weighing 1100 grams and a spleen practically as big, weighing 1000 grams. The surface of the liver was very coarsely nodular and on cutting through it we found large areas of scar tissue such as we are accustomed to find in the post atrophy type of cirrhosis and do not find in the alcoholic type of atrophic cirrhosis. The findings are almost identical with those of his brother except that they were obviously of a much more chronic type. There was a slight degree of acute necrosis as well. This was localized to small groups of cells and I should be inclined to think was analogous to the central necrosis which one often sees in streptococcus infection. You could not say it was central in this case because he did not have any recognizable lobules; the normal architecture had been completely obliterated by the irregularity of the regeneration. The kidneys were entirely normal and we could find no difference between the two. I think Dr. Richardson was justified in being cautious. The low position of the left one appeared to be due to the very large spleen, and the right one may well have gone up a little with the small liver. We did not find the focus of calcification. We did not know about that and did not look for it. I entirely agree with Dr. Jones in the interpretation of this patient's history.

DR. RICHARDSON: I should like to add that, on reviewing this case, I feel that I did not pay enough attention to the sudden onset and to the lack of great enlargement of the liver, both of which are definitely against a diagnosis of biliary cirrhosis.

The New England
Journal of Medicine

SUCCESSOR TO
THE BOSTON MEDICAL AND SURGICAL JOURNAL

Established in 1828

Published by THE MASSACHUSETTS MEDICAL SOCIETY under the jurisdiction of the

COMMITTEE ON PUBLICATIONS

R. I. LEE, M.D., *Chairman* HOMER GAGE, M.D.
R. B. OSGOOD, M.D. R. M. SMITH, M.D.
F. H. LAHEY, M.D.

EDITORIAL STAFF

JOHN P. SUTHERLAND, M.D. STEPHEN RUSHMORE, M.D.
GEORGE R. MINOT, M.D. HANS ZINSSER, M.D.
FRANK H. LAHEY, M.D. BENJAMIN WHITE, PH.D.
SHIELDS WARREN, M.D. HENRY R. VIETS, M.D.
GEORGE L. TOBEY, JR., M.D. ROBERT N. NYE, M.D.
C. GUY LANE, M.D. ROBERT M. GREEN, M.D.
WILLIAM A. ROGERS, M.D. CHARLES C. LUND, M.D.
JOHN F. FULTON, M.D. DWIGHT O'HARA, M.D.

ASSOCIATE EDITORS

GEORGE G. SMITH, M.D. WILLIAM B. BREED, M.D.
JOSEPH GARLAND, M.D.

WALTER P. BOWERS, M.D., *Managing Editor*
CLARA D. DAVIES, *Assistant Editor*

THE NEW HAMPSHIRE MEDICAL SOCIETY
PUBLICATION COMMITTEE

CARLETON R. METCALF, M.D. HENRY H. AMSDEN, M.D.
WARREN H. BUTTERFIELD, M.D.

THE VERMONT STATE MEDICAL SOCIETY
PUBLICATION COMMITTEE

WILLIAM G. RICKER, M.D. C. F. DALTON, M.D.
L. H. ROSS, M.D.

SUBSCRIPTION TERMS: *$6.00 per year in advance, postage paid for the United States, Canada $7.0½ per year, $8.52 per year for all foreign countries belonging to the Postal Union.*

Material for early publication should be received not later than noon on Saturday. Orders for reprints must be sent to the Journal office, 8 Fenway.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to The New England Journal of Medicine, 8 Fenway, Boston, Mass.

NEW HAMPSHIRE CANCER CONTROL

THE brief description of the New Hampshire State Cancer Commission and of its activities, which appears in this number of *The New England Journal of Medicine** is of interest, not only to those who are directly concerned in the cancer problem, but to the whole medical profession and to the community at large. It is a good example of the advantages which are to be obtained when the medical profession itself develops a well-studied plan for public health activity designed to supply needed medical service to the community. It is clear that the New Hampshire legislature has not only accepted these plans, but has supported them by appropriations of tax-funds sufficient to accomplish the desired results.

In cancer control, as in many other activities of life, the methods which are efficient and practicable in one State may not be immediately adaptable to the needs of another community. Massachusetts, New York, and other States have adopted legislation intended to provide more efficient service for the indigent and low-income cancer patient by very different and indeed much more expensive methods. The New Hampshire plan is worthy of study, even on this account alone; and many other States may find it desirable to adopt one or another of the features of the New Hampshire plan, when their legislative representatives are aroused to the necessity for providing more efficient service for the cancer patient.

In any case, it is widely recognized that education must play an important part in cancer control, over and above the provision of diagnostic and treatment service. Doctor Wilkins' statement makes it clear that the New Hampshire State Cancer Commission recognizes its educational responsibilities, both as regards the public and the medical profession. A brief medical handbook designed to remind physicians of the important aspects of the common forms of cancer and of recent advances in this subject is reprinted herewith, and the record of radio-talks and newspaper releases sponsored by the Commission in the past year is to be commended.

*See page 991.

PROGRESS AT McGILL UNIVERSITY

THE recent statement concerning the proposed reorganization of the medical school of McGill University[1] raises many interesting questions for discussion. What may be considered the starting point for the change is the recognition of the wisdom of requiring one year of interneship before the candidate is qualified to sit for the examination of a licensing board. The interneship is required (the statement says) in twenty-eight provinces and states before license, and by the change McGill formally enters the growing group of schools who not only recognize the importance of the interneship but insist that it shall become an essentially educational procedure, under the control and direction of some approved medical school. While alternatives are offered, it is expected "that in the majority of cases the postgraduate interne will be chosen as it is the most direct and economical pathway to practice".

The medical course is already long and arduous and it would seem that the addition of a year's interneship would prove a serious burden, but the fact of the situation is that without the insistence of boards of licensure or of schools of medicine, a very high percentage of recent graduates have voluntarily spent a year or more in hospitals. The requirement of the interneship by the school is then not an additional burden for most students, but the participation of the school in its control is certain to have a far-reaching effect in increasing the value of the experience.

Since ordinarily the interneship, whether voluntary or compulsory, does take a year in

addition to the medical course, McGill has telescoped, as it were, the five years of seven and one-half months each into four years of nine months each. This raises the old question of how long the academic year should be. Why six months or eight months or ten months? Is there not a great waste of time by the long vacations? It would be helpful if there were a study of the physiological and psychological reasons for the length of the medical course and for the distribution of time. The four quarter year looks like a great saving of time, but the intervals between quarters are in the case of most students too short for the needed recreation after intense application. Perhaps the physiology and psychology of study are too little understood and such long periods of "rest" would not be needed if work were done more in accordance with scientific methods.

There has long been a tendency on the part of medical students to spend much of the summer vacation in laboratory or hospital, for as a class they are eager to learn and do not spare effort to advance in their chosen field. Much is to be said in favor of letting them have free choice in spending their time outside of the formal periods of instruction, but if by so simple a rearrangement as McGill has made, a year's time can be saved in the medical course, the change is worth considering. If the medical course can be extended to nine months why not to ten? Then it would have almost the same content as at present and, including the internship, cover only four instead of five years. If the academic course were extended two months beyond the three years of ten months each, the full medical course would be of exactly the same content as at present but would be ten months shorter.

It may be that the physiological and psychological optimum is an eight months' academic year, but perhaps it is nine or ten. There is no scientific basis for the present scheme, however convenient it may be for some persons, and the experiment at McGill will be watched with great interest. It is a much needed step in the right direction.

REFERENCE

1. Science **83**: 296 (Mar. 27) 1936.

THE MEETING OF THE AMERICAN UROLOGICAL ASSOCIATION

BOSTON has been selected as the place for the thirty-third Annual Meeting of the American Urological Association, at the Hotel Statler, May 19-21, in response to the invitation of the New England Branch of the organization.

This is the largest and most active organized body of urologists in the world, with a membership of 966 active practitioners of this specialty, twenty honorary members, sixty Fellows, ten associate members and one corresponding member.

The geographical membership list includes 383 in the North Atlantic Section, 103 in the South Atlantic Section, 287 in the North Central Section, 82 in the South Central Section and 136 in the Western Section.

That Dr. George G. Smith of Boston is President of the Association is of particular interest to New England. The Committee of Arrangements, consisting of Drs. F. H. Colby, W. C. Quinby, J. D. Barney, R. F. O'Neil, J. H. Cunningham, A. Riley, A. H. Crosbie, and C. L. Deming, has been diligently at work arranging the details of the convocation.

The subcommittees are as follows: Entertainment: Drs. R. F. O'Neil, R. Chute, H. H. Howard, C. J. E. Kiekham; Ladies' Entertainment: Dr. R. Chute; Registration: Drs. G. C. Prather, B. E. Greenberg, E. L. Merritt, E. P. Stone; Golf: Drs. W. H. McNeil, Jr., E. G. Crabtree, C. S. Swan, E. J. O'Brien; Commercial Exhibits: Drs. C. J. E. Kiekham, J. B. Hicks, P. N. Papas; Scientific Exhibits: Drs. R. S. Ferguson, E. R. Mintz, H. H. Crabtree; Transportation: Drs. S. N. Vose, M. J. Hahn, Jr., B. D. Wetherell; Publicity: Drs. R. C. Graves, A. H. Crosbie, S. B. Kelley; Scientific Meetings: Drs. H. A. Chamberlin, S. B. Kelley, J. B. Hicks.

Unusual plans are under way for the entertainment of the wives and families of the members, with tours to the important historical and other attractive localities in and about Boston.

For those interested in golf, there will be a Tournament at the Woodland Country Club, Monday, May 18, preceding the Scientific Sessions, with a dinner and entertainment in the evening. Teas, luncheons and a Pop Concert by the Boston Symphony Orchestra will complete the social features. The ladies are invited to attend the annual banquet on the evening of May 20.

The American Urological Association was founded on February 22, 1902 at a meeting of the New York Genito-Urinary Society held at the residence of Dr. Ramon Guiteras, and Dr. Guiteras was elected the first President of the American Urological Association. The other officers elected as entered in the records of this first meeting are Dr. William K. Otis, Vice-President; Dr. John Vanderpoel, Treasurer; Dr. Ferd. C. Valentine, Secretary; and Dr. A. D. Mabie, Assistant Secretary.

The American Urological Association has active members residing in forty-four States of the Union and residents in Canada, Cuba, France, Hawaii, Porto Rico, and South America. There are honorary members in England, New Zealand, Germany, Italy, Holland, Belgium, Austria, France, Switzerland and Scotland.

An interesting function of this Association is its union with the American Association of Genito-Urinary Surgeons and the American Medical Association in the establishment of the American Board of Urology for the certification of urologists. An examination for this purpose will be conducted directly after the sessions this year in Boston.

This plan for the certification of specialists is being adopted by other medical societies and will be of value in giving assurance of competent service to the public.

The scientific sessions of the American Urological Association will be open to the general medical profession. Boston is honored in having these scientists meet here.

The Massachusetts Medical Society

SECTION OF OBSTETRICS AND GYNECOLOGY*

C. J. KICKHAM, M.D., *Chairman*
524 Commonwealth Ave., Boston, Mass.

R. S. TITUS, M.D., *Secretary*
472 Commonwealth Ave., Boston, Mass.

PREMATURE SEPARATION OF THE PLACENTA

From the standpoint of treatment, cases of premature separation of the placenta should be divided into cases of partial separation and cases of complete separation.

In partial separation the chief sign, and usually the only sign, is painless bleeding from the uterus. The diagnosis can be made only by determining that the bleeding is coming from within the uterus and that there is no placenta praevia present. Therefore, to establish a diagnosis beyond doubt, a vaginal examination is necessary. When the diagnosis is established the best treatment is immediate cesarean section, subject to two exceptions, which are noted below. When the diagnosis lies solely between partial separation of the placenta and placenta praevia and the case is one which would be treated by cesarean section were a placenta praevia present, a vaginal examination may be dispensed with, since the differentiation of the two conditions will have no effect on the plan of treatment. The exceptions referred to above are the following:

1. When the patient is not a pre-eclamptic or nephritic and her baby is nonviable and the bleeding is very slight or has stopped when the patient is first seen, delivery may well be postponed. If the bleeding stops, such cases will sometimes go to viability, or even to term, without any recurrence of bleeding. If delivery is postponed in such a case without vaginal examination, it must not be forgotten that the possibility of placenta praevia has not been excluded. When the baby is nonviable and the bleeding is severe or persistent, delivery should be effected by rupturing the membranes and packing the cervix and vagina as described below under complete separation of the placenta.

2. When the patient is well advanced in active labor at the time that partial separation occurs, immediate delivery through the pelvis is indicated if the state of the cervix is such as to permit this without risk to the mother. If the cervix is not fully dilated but can reasonably be expected to reach full dilatation shortly, the membranes should be ruptured, if they have not already ruptured, and pelvic delivery effected as soon as the cervix permits.

Complete separation of the placenta is known variously as abruptio placentae, ablatio placentae or uteroplacental apoplexy. It may occur following trauma, it may occur in association with pre-eclampsia, eclampsia or nephritis, and it may occur without apparent cause. It constitutes one of the very greatest obstetrical emergencies. The conspicuous symptom of complete separation is constant abdominal pain, frequently associated with severe pain in the lower back. In addition, in a typical fully developed case, there is marked tenseness and tenderness of the uterus. The fetal movements have ceased and the fetal heart cannot be heard. There is usually slight to moderate external bleeding, rarely profuse external bleeding and very rarely no external bleeding at all. The separation may occur very suddenly or it may occur gradually over a period of hours. In the latter case if there is little or no external bleeding at the beginning, close observation of the patient is necessary. Increasing distention, tonicity and tenderness of the uterus will establish the diagnosis.

In cases of complete separation of the placenta, the fetus is dead and the treatment is governed solely by the interests of the mother. Until a few years ago immediate cesarean section, with or without hysterectomy according to the condition and behavior of the uterus, was the treatment of choice in these cases. These patients, however, when they have pre-eclampsia or nephritis, are very poor surgical risks, being prone to develop anuria, and cesarean section in these cases gave a very high mortality. Much better results have been obtained in recent years by rupturing the membranes, packing the cervix and vagina tightly with gauze, applying a Spanish windlass to the abdomen and awaiting the onset of labor and delivery through the pelvis. If labor does not start promptly the uterus may be stimulated with repeated, small doses of

*A series of short selected articles by members of the Section is being published weekly.
Comments and questions by subscribers are solicited and will be discussed by members of the Section.

pitocin, which does not contain the blood pressure raising substance that is present in the whole extract of the posterior pituitary. In addition, the usual measures for combating preeclampsia should be instituted as described in a previous paper. Preparations should always be made for one or more transfusions, since these patients are frequently in considerable shock and are apt to bleed severely postpartum. If this procedure fails adequately to control the bleeding or labor does not progress so as to permit delivery within twelve or twenty-four hours, cesarean section may then be the only resort. Rarely severe and uncontrollable postpartum bleeding will necessitate hysterectomy.

THIRD ANNUAL POSTGRADUATE MEDICAL EXTENSION COURSE

The following sessions have been arranged by the Committee for the week beginning May 17:

Berkshire

Thursday, May 21, at 4:30 P.M., at the House of Mercy Hospital, Pittsfield. Subject: Pediatrics (Medical) — The Neonatal State. Instructor: J. L. Morse. Melvin H. Walker, Jr., Chairman.

Bristol North

Wednesday, May 20, at 7:30 P.M., at the Morton Hospital, Taunton. Subject: Ophthalmology and Otolaryngology. (a) The Major Hazards in Diagnosis of Diseases of the Eye, Ear, Nose and Throat as Seen in General Practice. (b) Special Treatment in Acute Medical and Traumatic Diseases of the Eye. Emergencies Arising in the Treatment of the Ear, Nose and Throat. Instructors: W. P. Beetham and C. H. Ernlund. Arthur R. Crandell, Chairman.

Franklin

Wednesday, May 20, at 8:00 P.M., at the Franklin County Public Hospital, Greenfield. Subject: Arthritis. (a) Medical Care of Patient in the Home. (b) Orthopedic Treatment in Hospital and Aids in Home Treatment. Instructors: T. H. Peterson and H. A. Nissen. Halbert G. Stetson, Chairman.

Middlesex East

Wednesday, May 20, at 4:00 P.M., at the Melrose Hospital, Melrose. Subject: Diseases of the Liver—Surgical Problems in Diagnosis of Acute Disease of Gall Bladder and Liver. Instructor: E. L. Young, Jr. Joseph H. Fay, Chairman.

Middlesex North

Friday, May 22, at 7:00 P.M., at the Lowell General Hospital, Lowell. Subject: Obstetrical Problems. Instructor: A. K. Paine. Leonard C. Dursthoff, Chairman.

Norfolk

Friday, May 22, at 8:30 P.M., at the Norwood Hospital, Norwood. Subject: Syphilis and Gonorrhea — Syphilis: Modern Treatment. The Use of Neosalvarsan, Tryparsamid, Bismuth, Mercury, Potassium Iodide, etc., in Office Practice. Gonorrhea: Treatment of Complications as Seen in General Practice. Instructors: O. F. Cox, Jr., and John Adams, Jr. H. B. C. Riemer, Chairman.

Worcester (Milford Section)

Wednesday, May 20, at 8:30 P.M., at the Milford Hospital, Milford. Subject: Pediatrics —Abdominal Disease in Childhood; Medical and Surgical Aspects. Instructors: P. H. Sylvester and T. H. Lanman. Joseph I. Ashkins, Sub-Chairman.

MISCELLANY

DR. WILBUR BECOMES PRESIDENT OF THE AMERICAN SOCIAL HYGIENE ASSOCIATION

Dr. Ray Lyman Wilbur, President of Stanford University, has been elected President of the American Social Hygiene Association. He succeeds Dr. Edward L Keyes, of New York, who resigned recently after serving for twelve years.—*Science*, May 1, 1936.

RECOGNITION OF DR. HUNT'S SIXTY-SIXTH BIRTHDAY

Dr. Reid Hunt, who retires from the professorship of pharmacology at the Harvard Medical School this year, celebrated his sixty-sixth birthday on April 20. On this occasion about fifty of his colleagues, former students and friends, gathered at the Harvard Club of Boston to do him honor. Dean C. Sidney Burwell was toastmaster. Short speeches were made by Dr. A. Lawrence Lowell, Professor James F. Norris, Professor Ross G. Harrison, Dr. K. K. Chen, Dr. Worth Hale and Dr. G. Philip Grabfield. Presentation was made of an etched portrait of Dr. Hunt, which will hang in the Medical School.—*Science*, May 1, 1936.

MAINE NEWS ITEMS

The subject of "State Medicine" is being vigorously discussed in Maine at the present time. A committee has been formed to make a comprehensive study of the medical needs of the state. It consists of representatives from the Maine Medical Association, from the Maine State Board of Health and from the Maine Planning Board.

This committee is to conduct a fact-finding survey of the State of Maine to determine just what medical service is available for the state, just what its needs are, and how these needs may be best supplied.

Dr. John L. Johnson of Bangor, President of the Maine Medical Association, gave a spirited talk before the Waterville Rotary Club recently.

He prefaced his remarks by stating that, "Largely

as a result of certain surveys made by certain Foundations, sociological and pseudosociological groups, and certain political groups, the idea has been fostered, and has grown, that a considerable proportion of the population suffers habitually from improper, or inadequate, medical care.

"However, these surveys do not in any instance tell us what medical care this part of our population lacks. They do not tell us whether many or any of these people seek medical care and cannot get it. It is probably true that there are isolated sections where people find it difficult, or even impossible, to get medical attention. It is certainly not true that this applies to even a moderate percentage of the population of the United States.

"It has been shown that State Medicine in other countries has not decreased the incidence of contagious disease, has not improved the health of the people and has not decreased the amount of loss of time due to illness, as well as has been done in the United States without State Medicine.

"In England the per capita daily loss of time due to illness has increased 38 per cent. In Germany it has more than doubled. In the United States it has remained stationary for a decade. State Medicine in European countries has never been brought about in response to any demand by the medical profession or any demand by the people, who supposedly lack medical care. State Medicine has always been proposed by and passed by the leaders of some political group to serve some political purpose."

In conclusion, Dr. Johnson stated that, "Until such time as the work of this committee shall be completed and their report and recommendations shall have been received, it would be distinctly unwise for the State of Maine to pass any legislation along these lines or to accept any legislation or any proposal along this line from the Federal Government."

The preliminary announcement of the Annual Meeting of the Maine Medical Association shows that it will be held at Rangeley Lakes, June 21, 22, and 23. The first meeting of the House of Delegates will be held the evening of the twenty-first.

The morning of the twenty-second will be devoted to sectional conferences and the afternoon to scientific papers.

The afternoon session on the twenty-third will be devoted to a symposium on Cancer, sponsored by the Cancer Committee of the Maine Medical Association.

The following papers will be presented:

Introduction, "Cancer in Maine," by Dr. J. W. Scannell, Chairman of Maine Medical Cancer Committee.

"Tumors, Defined and Classified," by Dr. J. Gottlieb, Pathologist, Central Maine General Hospital.

"Carcinoma of the Breast: Its Early Diagnosis, Prognosis and Treatment," by Dr. C. M. Robinson, Portland.

"Carcinoma of the Pelvis, Routine Examination, Symptoms, Diagnosis and Treatment," by Dr. M. Ridlon, Bangor.

"Carcinoma of the Gastro-Intestinal Tract: Its Early Symptoms, Diagnosis and Treatment," by Dr. E. H. Risley, Waterville.

"Pathology of Carcinoma of the Breast, Pelvis and Gastro-Intestinal Tract," by Dr. A. H. Morrill, Director, Diagnostic Laboratory, Augusta.

"X-Rays in Diagnosis of Malignant Tumors," by Dr. Forrest B. Ames, Bangor.

"Radium in the Treatment of Carcinoma," by Dr. William Holt, Portland.

"X-Ray Therapy in the Treatment of Malignancy," by Dr. S. A. Wilson, Lewiston.

Discussion of the Cancer Symposium, by Dr. Elliott C. Cutler and Dr. Soma Weiss of Boston.

There will be one speaker at the annual banquet on the night of June 23.

Dr. Frederick Thayer Hill of Waterville is the President-Elect for the coming year.

E. H. RISLEY, M.D.

BOSTON'S MENINGITIS MORTALITY

With the recent report of two more deaths from cerebrospinal meningitis in Boston, the total number is now forty since the first of the year.

SOCIAL SECURITY BOARD GRANTS $1,323,021 TO THREE NEW ENGLAND STATES

The Social Security Board announced May 8, 1936, that U. S. Treasury checks totaling $1,323,021.92 have been sent to three New England States with approved public-assistance plans. These checks represent the Federal share of the States' expenditures for assistance to their needy aged, during the three months ending June 30, 1936.

The New England States receiving checks, the amounts granted, and the estimated number of persons to be aided under the plan, according to data submitted by the States, are shown in the following table:

State	For Assistance to the Aged	
	Amount of check	Estimated number of persons to be aided
Massachusetts	$1,026,711.92	27,974
Connecticut	221,812.50	8,000
Vermont	74,497.50	4,300
Total	$1,323,021.92	40,274

LORD HORDER SAID:

It is possible, nay easy, to see a great number of patients and yet not see their diseases.

Science, like nature, never proceeds by leaps.

The human brain is the best machine of all.—*Bulletin*, New York State Medical Society.

RECENT DEATH

LULL—Henry Cushman Lull, M.D., formerly of Boston, died at his home on Brook Street, Kingston, Massachusetts, May 3, 1936. Dr. Lull was a native of Kingston, Massachusetts, the son of George W. and Helen Cushman Lull, and a direct descendant of Thomas Cushman one of the Mayflower group who settled in Plymouth.

He practiced in Boston for many years and had an office on Tremont Street. Dr. Lull was eighty-seven years of age at the time of his death and left no surviving relatives.

OBITUARY

FREDERICK DANFORTH McALLISTER, M.D.

Frederick Danforth McAllister, M.D., was born in Lawrence, the son of John G. McAllister, M.D., a Lawrence physician, on October 2, 1872, and died at the Lawrence General Hospital on March 17, 1936, twelve hours following an operation for an acute gangrenous gall-bladder.

He was graduated from the Lawrence High School in 1890, Amherst College in 1894, and Harvard Medical School in 1898. His internship was at the Worcester City Hospital, where he worked with a staff of eminent physicians to whom he looked back with much pleasure, and whose influence undoubtedly was of great aid in his later professional life.

On December 29, 1899, he was elected a candidate for house physician for six months beginning January 1, 1900, at the Lawrence General Hospital, then located on Methuen Street.

On May 28, 1900, he was elected to membership on the Medical Staff of the Lawrence General Hospital.

At the opening of the present Lawrence General Hospital in 1903, on the Russell Estate, he began to carry a three months' surgical ward service, and performed this annual duty up to the time of his death.

Dr. McAllister was noted for his good judgment and sound knowledge of diagnosis and treatment, including operative procedure. He was another of those physicians, on the Medical Staff of the Lawrence General Hospital, of whom it could be said always that the patient's interests were perfectly safe in his hands.

Dr. McAllister was Secretary of the Medical Staff from 1923 until he died.

His life was upright as should become a professional man, and the Medical Staff of this Hospital hereby expresses a feeling of loss at his untimely death.

He was a member of the Lawrence Medical Club, a Fellow of the Massachusetts Medical Society, American Medical Association and American College of Surgeons.

His immediate surviving relatives are his widow, a daughter, a brother and two sisters.

Your committee closes this memorial with a quotation furnished by his brother, Rev. Frank B. McAllister, and attributed to John Brierley:

"May we not say of death itself that it is the final and effective remedy? On the physical side it is kindly Nature's way out of an impossible situation. It is heroic surgery. When the forces of disease have prevailed against her ordinary methods of healing, she dissolves in this way a combination that has become simply painful. Nothing has been destroyed. What has happened is that the arrangement of particles round a hopelessly weakened center has to come to an end, leaving these particles free, for a new and sounder grouping."

Geo. B. Sargent, M.D.,
V. A. Reed, M.D.,
J. Forrest Burnham, M.D.
Committee: Medical Staff,
Lawrence General Hospital.

NOTICES

AN OMISSION

In the list of certified Massachusetts Psychiatrists from which the news item "The Certification of Massachusetts Psychiatrists" which appeared on page 956 of our issue of May 7, was taken, the name of Dr. Riley H. Guthrie did not appear. Dr. Guthrie is duly certified as a Psychiatrist.

REMOVAL

Louisa Paine Tingley, M.D., announces the removal of her office to 416 Marlborough Street, Boston, Telephone Kenmore 0822.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF BIOLOGY AND PUBLIC HEALTH

Announcement of a Special Public Health Course

A special course of training will be offered this year from June 4 to July 3, inclusive, for men and women interested in public health work. The course will be given as part of the training now being offered to students in residence at M. I. T. under the Federal Social Security Act.

Instruction will be given in the following subjects: Public Health Administration, Epidemiology, Vital Statistics, Communicable Diseases and Public Health Problems.

The work in Public Health Administration will include the organization and activities of municipal, county, state and federal health agencies; public health surveys; organization of public health campaigns; and the use of the city and rural health appraisal forms.

The course in Communicable Diseases will consider the biology of disease and the theories of immunity. Special instruction will also be given in the organization and conduct of the community program against tuberculosis.

In Epidemiology, the sources of infection, modes of

spread of disease, the methods employed in studying and controlling epidemic diseases, and the lessons to be learned from analyses of specific epidemics will be considered.

Vital statistics will consider the sources of statistical information, methods of collection, computation of rates, tabulation, graphical presentation, analyses and interpretation.

Under Public Health Problems, special assignments will be made for study, analyses and group consideration. Current public health problems discussed in the professional journals and daily press will also be presented and discussed.

Classes will be held daily from 9 A.M. to 12:00 M., and 2 to 3 P.M., exclusive of Saturdays and Sundays.

The registration fee is $5.00. Tuition fee, $70.00 (Total $75.00).

Inquiries should be addressed to the Department of Biology and Public Health, Massachusetts Institute of Technology, Cambridge, Mass. Registration material will be sent on request.

UNITED STATES CIVIL SERVICE EXAMINATIONS

Medical Officer (Specialist in Venereal Disease Control)

Medical Officer (Specialist in Cardiovascular-Renal Disease)

$3,800 a Year

Applications must be on file with the United States Civil Service Commission at Washington, D. C., not later than May 25, 1936.

The United States Civil Service Commission announces open competitive examinations for the positions named above. Vacancies in these positions in the field and in positions requiring similar qualifications will be filled from these examinations, unless it is found in the interest of the service to fill any vacancy by reinstatement, transfer, or promotion.

REPORTS AND NOTICES OF MEETINGS

SOUTHEASTERN MASSACHUSETTS ASSOCIATION OF BOARDS OF HEALTH

The spring meeting of the Southeastern Massachusetts Association of Boards of Health was held in Hyannis on Wednesday, April 22, with some thirty members present representing fifteen towns of the district. The principal speaker was Dr. Gaylord W. Anderson of the State Department of Public Health, and his subject Milk-Borne Epidemics.

Dr. Anderson addressed his remarks directly to the health officer, outlining the principles of prevention, and emphasizing the necessity of the pasteurization of milk, using through his paper the simile of the steamship without the customary safety precautions, life boats, life preservers, special details of construction, etc. It might make its voyages for a while without accident, but should one occur there would be criticism, and the question would be asked, "Why was not this prevented?"

It is true that milk-borne epidemics are not common, in fact they might be termed rather rare, but when they do occur they attract widespread attention, and there is regret that means of prevention have not been taken. In communicable diseases as in the case of the steamship, we should profit by the unfortunate experience, and take precautions against future repetition of the disaster. It is one of the duties of a board of health to protect the public, and to effect this, it should become better acquainted with the causes of diseases.

There are three general classes into which milk-borne diseases may be divided, based on the mode of transmission. First there are diseases of the cow, e.g., tuberculosis, and here the speaker complimented the Cape for its pioneer work in the prevention of tuberculosis in its cows. Secondly, the cow may be infected from man, and thirdly, there are cases in which the cow is not involved, the infection coming from man, directly or through unsanitary conditions in the handling of the milk.

The principal diseases of the cow, which may be communicated through milk, are tuberculosis and undulant fever. The former, through the elimination of infected cattle, has almost reached the vanishing point in localities in which only tuberculin-tested cows are permitted. Cape Cod, as has already been noted, is a leader in requiring this precaution. Undulant fever is not at all common, but is likely to attract much more attention when more generally recognized. It is now widespread, but is not diagnosed in the majority of cases. It could be controlled by cutting off the supply of milk from "diseased" cows, but there are several obstacles. If carried out to the letter it would be likely to cause a shortage of milk. The testing of the cows to determine whether they are infected would be exceedingly difficult. Even if the cow is infected, its milk may not contain the specific germ. If it does, this may prove to be an intermittent rather than a constant condition. Then again, just what the effect on man may be is not certain. Some human beings readily contract the disease, but in other cases small doses of infected matter seem to result in immunization. These facts suggest some of the difficulties in any program of prevention due to the cow.

Forty-two cases of undulant fever were reported last year in the state, but this is by no means the full number, for physicians are not yet at all familiar with it, while in its milder forms it is likely to attract little attention. Comparatively few of the cases are fatal, but debilitating effects of the disease may last for a long time. Medical authorities are now busily at work trying to solve some of these problems. Meanwhile pasteurization of milk furnishes an important step toward reasonable safety.

In the second group, cows become infected with some diseases through contact with man, septic sore throat, scarlet fever and diphtheria among them. Milk, which is such a good food for man and ani-

mals, is equally nourishing to many of the lower organisms, and disease germs multiply rapidly in it. Communities using a milk infected with septic sore throat, for example, develop many cases, and there have been some startling outbreaks. A number of local ones were noted by Dr. Anderson, one of which was in a town of 4,000, which developed 900 cases with 48 deaths. In another instance, 25 persons used the milk from an infected cow. Of these, 18 became sick and two died, while members of the group carried the infection to two other towns, one of them forty miles distant from the place of original infection.

"Now what are the chances of prevention here?" queried the speaker. To take cultures of the milkers and handlers, is not practicable, and might after all tell only part of the story. Bacterial analysis of the milk would not reveal the presence of the germ early enough to prevent infection, while examination by a veterinarian, although good in principle, is too cumbersome, since a daily examination may be necessary. There is only one way to be sure in cases like these, namely, to pasteurize the milk.

What is true of septic sore throat applies practically to scarlet fever, and this demands the same measure of general protection, pasteurization. So far as Massachusetts is concerned milk-borne diphtheria is rare with no cases in the past ten years, but it is more of a problem in some other places.

In the third group are maladies, communicated to the milk by human beings, among which are typhoid and dysentery, with some septic sore throat and scarlet fever. There are occasional outbreaks of typhoid due to the use of raw milk, the presence of a carrier or some unsanitary procedure, such as neglect in the disposal of sewage, failure to protect the water supply used for washing utensils or carelessness on the part of individuals.

Theoretically, the ordinary measures of prevention should care for these troubles, but there are a number of practical difficulties. A person may be affected mildly by typhoid, or may just be coming down, or indeed be a carrier, without being aware that he has had the disease. Cultures are very variable and in fact are not always reliable. Back of all this as a method of prevention is the health education of the people, whereby the food handler may eliminate all risks from personal carelessness or from unsanitary conditions. With milk it is absolutely necessary to have clean cows, clean milkers, and clean handling into clean bottles. And then, as a superimposed protection, pasteurization. This is not, as it is sometimes improperly characterized, the cleaning up of dirty milk, but the safeguarding of milk against possible infection through factors not always otherwise to be controlled. It is not a substitution for sanitation, but is a reasonable means of prevention of various communicable diseases that are due to the use of raw or contaminated milk. "Make sure by pasteurization," said Dr. Anderson in conclusion.

The round-table discussion by the health officers, which usually closes these meetings, was based at this session on a question by the secretary, Mr. George F. Crocker, Jr., who is district milk inspector. It concerned the attitude which the health board should take toward a new milk distributor, who seeks to establish himself in a place already well supplied with milk. After considerable discussion it was the consensus that, if the requirements with which the law surrounds such an application are completely fulfilled, and they should be for every town interested, the board of health has no option if the milk comes up to the standard. It is then purely a commercial question, and should be considered by the local chamber of commerce or official business organization.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held at 4:30 P.M., May 25, 1936, in the Amphitheatre of the Children's Hospital, Boston, Mass. Program: 1. An Identical Twin Presenting a Bicuspid Pulmonic Valve. Dr. Harry Dietrick. 2. Two Cases of Idiopathic Hypertrophy of the Heart with Recovery. Dr. Mark I. Makler. 3. Arachnodactylia. Dr. Hyman Green. 4. A Case for Diagnosis. Dr. Henry F. Keever. 5. Behavior Difficulties in Children Who Have Attended Heart Clinics. Dr. Bronson Crothers. 6. Some Cases of Transposition of the Great Vessels. Dr. Paul W. Emerson. 7. A Definite Clinical Syndrome Associated with Enlargement of the Heart in Infants and Young Children. Dr. M. A. Kugel (Mt. Sinai Hospital, New York).

All members of the New England Heart Association and interested physicians are cordially invited to attend.

JAMES M. FAULKNER, M.D., *Secretary.*

AMERICAN UROLOGICAL ASSOCIATION

PROGRAM

TUESDAY, MAY 19, 1936—9:00 A.M.-12:30 P.M.

Surgical Procedures in Neurodynamic Pathology of the Upper Urinary Tract. William P. Herbst, Washington, D. C.

The Present Status of Renal Sympathectomy. Thomas E. Gibson, San Francisco, California.

Discussion: Lawrence R. Wharton, Baltimore, Maryland.

Hypernephroma. Lawrence T. Price, Richmond, Virginia.

Irradiation and Malignant Renal Disease; Effect of Irradiation on the Acquired Single Kidney. Arbor D. Munger, Lincoln, Nebraska.

Hemorrhagic Cyst of the Kidney. J. Dellinger Barney, Boston, Massachusetts.

Discussion: Archie L. Dean, Jr., New York City.

An Experimental Study of Injuries of the Upper Urinary Tract. W. Calhoun Stirling and A. Lands (by invitation), Washington, D. C.

Diagnosis and Treatment of Trauma of the Kidney. Austin H. Wood, Baltimore, Maryland.

Discussion: Nathaniel P. Rathbun, Brooklyn, New York; Miley B. Wesson, San Francisco, California.

Renal Atrophy. Robert E. Cumming, Detroit, Michigan.

The Atrophic or Hypoplastic Kidney. F. G. Harrison, Philadelphia, Pennsylvania.

Discussion: William F. Braasch, Rochester, Minnesota; Elmer Hess, Erie, Pennsylvania.

TUESDAY, MAY 19, 1936—2:00 P.M.-5:30 P.M.

The "Cord Bladder." Definition, Treatment, and Prognosis When Associated with Spinal Cord Injury. Donald Munro, Visiting Surgeon for Neurosurgery, the Boston City Hospital, Boston, Massachusetts. (By invitation.)

The Diabetic (Cord) Bladder. Richard D. Gill, Wheeling, West Virginia.

The Technic of Suprapubic Cystotomy for Drainage. Montague L. Boyd, Atlanta, Georgia.

Discussion: Paul A. Ferrier, Pasadena, California; Irving Simons, New York City.

The Ureteral and Renal Complications of Carcinoma of the Cervix. Roger C. Graves, Charles J. E. Kickham, and Ira T. Nathanson (by invitation), Boston, Massachusetts.

Vascular Obstruction of the Ureter in Children. Meredith F. Campbell, New York City.

Supernumerary Ureters with Extravesical Openings. Henry Dawson Furniss, New York City.

Discussion: Roy B. Henline, New York City; Fletcher H. Colby, Boston, Massachusetts.

Demonstrations

A New Cystometer Devised to Minimize the Present Difficulties. David W. MacKenzie and Sidney Beck (by invitation), Montreal, Canada.

An Improved Filiform Guide. Floyd C. Hendrickson, Canton, Ohio.

Transurethral Prostatotomy for Relief of Prostatic Abscesses and Acute Obstructive Prostatitides with an Electro-Prostatome. Gideon Timberlake, St. Petersburg, Florida.

WEDNESDAY, MAY 20, 1936—9:00 A.M.-12:30 P.M.

The Relationship Between the Chemical Composition of Renal Calculi and Associated Bacteria. James T. Priestley, Rochester, Minnesota.

A Study of Recurrence Following Operations for Nephrolithiasis. Francis Patton Twinem, New York City.

Factors Determining the Management of Ureteral Stones; an Improved Method of Their Cystoscopic Removal. Thomas D. Moore, Memphis, Tennessee.

Discussion: Fuller Albright, Boston, Massachusetts; Linwood Keyser, Roanoke, Virginia.

Cystitis Emphysematosa. N. L. Burrell, Springfield, Ohio.

The Treatment of Incrusting Alkaline Cystitis. Alexander Randall and Edward W. Campbell, Philadelphia, Pennsylvania.

Discussion: William E. Stevens, San Francisco, California.

Further Developments in the Surgery of the Prostate. Joseph F. McCarthy, New York City.

Mortality in Prostatic Surgery. Harry C. Rolnick and Lester A. Riskind (by invitation), Chicago, Illinois.

Discussion: Gilbert J. Thomas, Minneapolis, Minnesota; I. G. Duncan, Memphis, Tennessee; Nathaniel G. Alcock, Iowa City, Iowa.

The Founding of the American Urological Association, with Tribute to Its Founder. Colin Luke Bett, New York City.

WEDNESDAY, MAY 20, 1936—2:00 P.M.-5:30 P.M.

President's Address

Dr. George Gilbert Smith, Boston, Massachusetts

The Ramon Guiteras Lecture: "The Influence of Infection of the Lower Urinary Tract and Reproductive Organs on the Kidneys; with Special Reference to Lithiasis and Hydronephrosis." Mr. H. P. Winsbury-White, London, England.

Discussants: Hugh Hampton Young, Baltimore, Maryland; Hugh Cabot, Rochester, Minnesota; J. Dellinger Barney, Boston, Massachusetts; Henry G. Bugbee, New York City; William E. Lower, Cleveland, Ohio.

Business Meeting. (To follow.)

Banquet: 8:00 P.M.

THURSDAY, MAY 21, 1936—9:00 A.M.-12:30 P.M.

Cocaine Absorption in the Urethra and Bladder; a Report on Quantitative Determinations. Ernest Rupel and R. N. Harger (by invitation), Indianapolis, Indiana.

Incontinence in the Male and Female, with a New Operation for Its Relief. Oswald Swinney Lowsley, New York City.

A Histo-Pathological Study of the Female Bladder Neck and Urethra. David W. MacKenzie and Sidney Beck (by invitation), Montreal, Canada.

Discussion: Alfred I. Folsom, Dallas, Texas; Thomas J. Kirwin, New York City.

X-Ray Therapy in the Treatment of Bladder Tumors. Albert E. Bothe, Philadelphia, Pennsylvania.

Infiltrating Carcinoma of the Bladder. J. A. Campbell Colston and W. F. Leadbetter (by invitation), Baltimore, Maryland.

The Grading of Bladder Tumors. Major Raymond O. Dart, Army Medical Museum, Washington, D. C. (By invitation.)

Five-Year End Results in the Bladder Tumor Registry. Russell S. Ferguson, New York City, Chairman of the Carcinoma Registry Committee of the American Urological Association.

Discussion: Benjamin S. Barringer, New York City.

Enterovesical Fistula. Charles C. Higgins, Cleveland, Ohio.

Primary Carcinoma of the Seminal Vesicle. Andrew McNally and Frank M. Cochems (by invitation), Chicago, Illinois.

Discussion: James F. Balch, Indianapolis, Indiana.

THURSDAY, MAY 21, 1936—2:00 P.M.-5:30 P.M.

Heminephrectomy. Its indications and Limitations. Elmer Hess, Erie, Pennsylvania.

Resections of the Kidney. Benjamin S. Abeshouse and Albert E. Goldstein, Baltimore, Maryland.

Unsuccessful Plastic Operations for Hydronephrosis. John K. Ormond, Detroit, Michigan.

A Simple Method for Doing Nephropexy. Charles M. McKenna, Chicago, Illinois.

Discussion: William C. Quinby, Boston, Massachusetts; Edwin Beer, New York City.

How Prevalent Are Smegma Bacilli? Their Alleged Importance as a Confusing Factor in the Examination of Urine for Tubercle Bacilli by the Centrifugal and Smear Methods. Howard S. Jeck and Charlotte Hanley (by invitation), New York City.

Impotence and Masturbation from the Urological Point of View. Max Huhner, New York City.

The Surgery of Genital Elephantiasis (nontropical). Ernest M. Watson, Buffalo, New York.

Discussion: Winfield W. Scott, Rochester, New York; David M. Davis, Philadelphia, Pennsylvania.

NEW ENGLAND PHYSICAL THERAPY SOCIETY

ANNUAL MEETING

The Annual Meeting of the New England Physical Therapy Society will be held at the Hotel Kenmore, Boston, on Wednesday evening, May 20, 1936, at 8 o'clock.

PROGRAM

Business Meeting:
Reports of Officers.
Reports of Committees.
Election of Officers.

Scientific Program:
Injection Treatment of Varicose Veins, Technic and Results. (Motion pictures will be shown.) DeWitt G. Wilcox, M.D., Professor Emeritus of Gynaecology, Boston University Medical School.
Discussion: Herbert G. Dunphy, M.D., Member Surgical Staff, Boston City Hospital and Newton Hospital.
Question Period.

The Council will meet promptly at six o'clock.
Informal Round Table Dinner at six-thirty o'clock.
As this is the last program to be given by the Society until October it is hoped that all members will make a special effort to be present.

Members of the medical profession are cordially invited to attend.

WILLIAM D. MCFEE, M.D., *Secretary.*
Boston, Massachusetts.

TRUDEAU SOCIETY

A meeting of the Trudeau Society will be held on Thursday, May 21, at 4 P.M., at the North Reading State Sanatorium, North Wilmington, Mass. Dr. David Zacks of the Chadwick Clinics will speak on Asymptomatic Tuberculosis. Drs. Earle C. Willoughby, Rufus R. Little and Anna H. Maxwell will discuss Treatment of Tuberculosis by Means of Collapse Therapy in Children under Seventeen Years of Age. Dinner will be served at 6:30 P.M.

MOSES J. STONE, M.D., *Secretary.*

THE NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The eighth spring meeting of the New England Obstetrical and Gynecological Society is to be held on Thursday, May 28, 1936, at Providence, R. I. The following program has been arranged:

Following the morning and afternoon hospital activities, the Society dinner will be held at the Squantum Club.

MORNING PROGRAM

Registration at Rhode Island Medical Society Library, 106 Francis Street

Providence Lying-In Hospital:

9-10—Inspection of hospital.
10-10:30—Management of 100 cases of Placenta Praevia at the Providence Lying-In Hospital. Dr. John G. Walsh.
10:30-11—Treatment of Heart Disease complicating Pregnancy and Labor in 609 cases at the Providence Lying-In Hospital. Dr. Frank T. Fulton.
11:15-11:45—Treatment of Premature Infants with demonstration of an inexpensive oxygen box. Drs. Buffum and Lord.
11:45-12:15—Deduction to be drawn from 108 Maternal Deaths at the Providence Lying-In Hospital. Dr. E. S. Brackett.
1:00 — Luncheon. Guests of Providence Lying-In Hospital.

Rhode Island Hospital:

9-11—Operating clinic. Drs. Sweeney, Buxton and Gynecological Staff. There will also be available for those who wish to see them, other operations by the general surgical service.
11:00—Dry clinic in the Peters House Auditorium, Rhode Island Hospital.
11-11:30—Presacral nerve resection. Report of cases with lantern slides. Dr. George W. Waterman.
11:30-12:15 — Panhysterectomy vs. supercervical hysterectomy with report of a series of cases. Dr. Thomas W. Grzebien.
Discussion by Drs. Waterman and Clarke.

12:15-12:45—Gonorrhea in the Female. Dr. John F. Murphy.

12:45 — Luncheon as guests of the Rhode Island Hospital.

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, MAY 18, 1936

Monday, May 18—

*10 A.M., 2 P.M., 7:30 P.M. The American Neisserian Medical Society. Hotel Statler.

*2-4 P.M. Surgical Lecture at the Peter Bent Brigham Hospital Amphitheatre, by Dr. K. H. Glertz.

Tuesday, May 19—

American Urological Association. Hotel Statler.

*9-10 A.M. Boston Dispensary, 25 Bennet Street, Boston. Clinical Diagnosis of Jaundice. Dr. Howard M. Clute.

9:30 A.M. Massachusetts General Hospital. Thoracic Clinic. Ether Dome.

11:30 A. M. Massachusetts General Hospital. Nerve Eye Conference. Out-Patient Department.

12 M. South End Medical Club. Office of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

2:30 P.M. Pediatric Ward Visit. Massachusetts Eye and Ear Infirmary.

Wednesday, May 20—

American Urological Association. Hotel Statler.

8 A.M. Massachusetts General Hospital. Grand Rounds. Orthopedic Department.

*9-10 A.M. Boston Dispensary, 25 Bennet Street, Boston. Hospital Case Presentation. Dr. S. J. Thannhauser.

†12 M. Clinico-Pathological Conference. Children's Hospital.

*2-4 P.M. Surgical Lecture at the Peter Bent Brigham Hospital Amphitheatre, by Dr. K. H. Glertz.

Thursday, May 21—

American Urological Association. Hotel Statler.

8 A.M. Massachusetts General Hospital. Circulatory Clinic. Ward F.

*8:30-9:30 A.M. Clinic, Surgical and Orthopedic Staffs of the Children's Hospital, at the Children's Hospital.

*9-10 A.M. Boston Dispensary, 25 Bennet Street, Boston. Social Service Case Presentation. Miss Edith Canterbury.

9:15 A.M. Massachusetts General Hospital. Neurological Conference. Ether Dome.

12 M. Massachusetts General Hospital. Clinico-Pathological Conference.

Friday, May 22—

*9-10 A.M. Boston Dispensary, 25 Bennet Street, Boston. Newer Aspects of Diabetes. Dr. Reginald Fitz.

12 M. Massachusetts General Hospital. Clinical Meeting of Staff of the Children's Medical Service. Ether Dome.

12 M. Massachusetts General Hospital. Urological Conference. Out-Patient Department.

Saturday, May 23—

*9-10 A.M. Boston Dispensary, 25 Bennet Street, Boston. Hospital Case Presentation. Dr. S. J. Thannhauser.

*10 A.M. - 12 M. Staff Rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.
†Open to Fellows of the Massachusetts Medical Society

May 15—Boston University School of Medicine Surgical Clinic, Boston City Hospital. See page 901, issue of April 30.

May 18—Springfield Medical Association, 8:30 P.M. at the rooms of the Springfield Academy of Medicine, 20 Maple Street. The Development of Medicine in the United States, 1636-1936. Dr. Henry E. Sigerist.

May 18—The American Neisserian Medical Society. See page 811, issue of April 16.

May 18, 20, 25—Surgical Lectures at the Peter Bent Brigham Hospital by Dr. K. H. Glertz. See page 957, issue of May 7.

May 19—The South End Medical Club. See page 958, issue of May 7.

May 19-21—American Urological Association. See page 1014.

May 20—New England Physical Therapy Society. See page 1016.

May 21—Trudeau Society. See page 1016.

May 25—New England Heart Association. See page 1014.

May 28—New England Obstetrical and Gynecological Society. See page 1016.

May 31 - June 1—International Cardiological Meeting, Royat (Auvergne) Assembly of Physiologists, Pathologists and Therapeutists. See page 754, issue of April 9.

June 4 - July 3—Massachusetts Institute of Technology Department of Biology and Public Health. See page 1012.

June 15-19—The Executive Board of the Catholic Hospital Association will meet at the Fifth Regiment Armory, Baltimore, Md.

June 16-July 28—Summer Course in Bacteriology. See page 385, issue of February 20.

June 29 - July 11—Hospital Administration. See page 957, issue of May 7.

September, 1936 — First International Conference on Fever Therapy. See page 1325, issue of December 26, 1935.

September, 1936—First International Congress of Sanatoria and Private Nursing Homes. See page 803, issue of April 16.

September 7-10—International Union against Tuberculosis. See page 554, issue of March 12.

October 19-23—Clinical Congress of the American College of Surgeons. See page 180, issue of January 23.

DISTRICT MEDICAL SOCIETY

PLYMOUTH DISTRICT MEDICAL SOCIETY

May 21—Lakeville State Sanatorium.

G. A. MOORE, M.D., Secretary.
167 Newbury Street, Brockton.

BOOK REVIEWS

National Medical Monographs. Diseases of the Chest. J. Arthur Myers. 285 pp. New York: National Medical Book Company, Inc.

The author of this book has been connected with the Lymanhurst School in Minneapolis for the past fourteen years. He has had an opportunity there to study the problem of "childhood tuberculosis" in 12,000 children. This work has given him a wide reputation, and in 1934 the National Tuberculosis Association presented him with its Trudeau Medal. Therefore, anything that Dr. Myers writes on the subject of tuberculosis has the stamp of authority.

The present volume consists of 360 small pages, 200 of which are devoted to tuberculosis. The author writes in outline form with summaries at the end of each chapter. He makes his points with unusual clearness. Any student of the tuberculosis problem who has not read Dr. Myers' previous works should hasten to read this latest summary of his views. In former publications, particularly in his books entitled "Tuberculosis Among Children" and "The Child and the Tuberculosis Problem", the author has covered much of the same ground. The present volume deals with adult as well as childhood tuberculosis, and takes up artificial pneumothorax treatment in addition to other phases of the general problem. It also shows certain changes in the author's viewpoint.

In the opinion of the reviewer, this discussion of tuberculosis represents the author's best work and

is in every way a masterly production. This does not mean that everyone will agree with his opinions, and probably the majority of critics will feel that he has failed as yet to prove his favorite thesis—that a first infection with tubercle bacilli sensitizes an individual toward later reinfection without producing an appreciable immunity. However, most readers will agree with Myers that infection with tubercle bacilli should be avoided at all ages. Again, all will not agree that this necessarily means handling cases of tuberculosis in the hospitals as if they were cases of acute contagious disease. There will be debate also as to the degree of risk assumed by doctor and nurse in caring for the patient ill with tuberculosis.

The second part of the book attempts to cover, in 160 small pages, the problems of "Pneumonia; Suppurative Conditions of the Bronchi, Lungs, and Pleurae; Tumors within the Thorax; Massive Collapse, Foreign Bodies, Spontaneous Pneumothorax, and Pulmonary Embolism; Diseases Due to Other Mould-like Bacteria, True Moulds, and Yeast-like Fungi; and Diseases and Conditions Caused by Inhalation of Dust." The author gives a good summary of the high spots of present opinion on these problems, but so short a discussion is of little value to either student or practitioner. The book hardly deserves the title, "Diseases of the Chest".

Individual Exercises. Selected exercises for individual conditions. George T. Stafford, Harry B. DeCook, and Joseph L. Picard. 111 pp. New York: A. S. Barnes & Company. $1.00.

This paper-covered book of some 100 pages is designed chiefly for laymen and women. The Preface urges that before these exercises are taken, the individual should first place himself in the hands of his physician and obtain a correct diagnosis of his condition. Once this is made, the authors believe that the individual himself can then select his exercise program from the sets described in the book. There follows Chapter I on "The Need for Exercise in Present-Day Society" and in subsequent chapters there are dissertations on Blood Pressure, Constipation, Digestive Disorders, Foot Disturbances, Heart Disturbances, Hernia, Infantile Paralysis, Kidney Disorders, Knee Disturbances, Malnutrition, Mental Disorders, Posture, Ptosis, Neurasthenia and Scoliosis. With each dissertation sets of progressive exercises are suggested.

The authors have not escaped certain pitfalls which are always met when diseases and lesions are discussed with the laity by other members of the laity. The authors have had much contact with physicians and appear to be men especially well trained for the important positions which they hold. Under infantile paralysis, for example, this difficult subject of muscle training would be better left to physicians to describe. There is definite danger of too much dogmatism in the description of knee disturbances and under posture no special attention is paid to the method of correcting the prevailing faults of body mechanics. Scoliosis is in the reviewer's opinion a disease in which there is quite as much danger for over- as for underexercise, since there is the possibility that a well compensated and fairly rigid curve will increase if the spine is made too flexible. Chapter IV is entitled "Maintaining Health or Keeping Physically Fit" and there follows a proposed health scale which patients may check consisting of (A) a personal health score of twenty points and (B) health habits of fifty-six points, with the opportunity for a check-up six months after the exercises are started. This is not a bad idea but probably hardly allows for the frailties of human nature.

Chapter V, which comprises a little more than half the book, is made up of 100 exercises with stickpin illustrations and fairly easily grasped instructions.

The advice is constantly given that those taking the exercise should consult their physicians and obtain a diagnosis. We believe that the physician himself should prescribe at least the type of exercises and should be the one to watch the effect, not only the corrective effect, but the effect on the patient's general condition.

As a calisthenic manual, this book will be found useful for the average man or woman who does not require careful medical supervision.

Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes, and Tonsils. Francis H. Williams. 118 pp. Boston: The Stratford Company. $2.00.

This little book is a summary of the work of one of the pioneers in radium therapy. Dr. Williams began experimenting with radium in 1900, two years after its discovery by Madame Curie. He learned to separate the beta rays from the gamma rays, found out what screening was necessary to cut out the beta rays and demonstrated that gamma rays passed through the body sufficiently to illuminate a fluorescent screen. His first clinical use was on a case of psoriasis where he found that the beta rays destroyed the lesions, but the gamma rays did not.

Over a period of thirty years the writer has been using radium in skin diseases, new growths of the skin, spring catarrh of the conjunctiva, new growths of the eyelids, opacities of the cornea, cataracts and enlarged tonsils. The technique used in each of these conditions is described, together with some of the results. Sufficient data are not given to tell us what per cent of the cases treated for a given disease showed improvement or were cured.

This book is excellent as a report of what one man has been able to do with radium. The methods of treatment of skin cancer and the doses used are not detailed enough to teach another physician to use radium. The reviewer does not agree with all the writer's statements or with some of his methods of treatment and wonders if sufficient attention has been given to newer methods which have been developed. He finds it difficult to explain why Dr. Williams can cure cataracts when so many other radiologists have found that they are quite unresponsive.